

Acta Genetica et Statistica Medica

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INTRODUCTION

Professor *Gunnar Dahlberg*, the founder and editor of «Acta Genetica et Statistica Medica», died in Uppsala on July 25th, 1956.

From the foundation of the journal in 1948, *Otto Lous Mohr*, Oslo, and *Tage Kemp*, Copenhagen, were associate editors. After Professor *Dahlberg's* death *Otto Lous Mohr* retired from his post as co-editor, leaving *Tage Kemp* as the only remaining editor. «Acta Genetica et Statistica Medica» has been published throughout by S. Karger, Ltd., Basel and New York.

In his introduction to the first volume, *Gunnar Dahlberg* emphasised that this periodical would have a special appeal for medical men, but would not neglect the interests of those geneticists who were concerned with wider aspects of human genetics. This programme will be maintained in the future. The journal will continue to deal with all aspects of medical genetics as well as those subjects within the field of human genetics in general which play an important role in medical research, thus constituting a link between medicine, genetics, demography and anthropology.

Amongst the subjects to be covered in this journal may be mentioned: methods in medical and human genetics, including demography and medical statistics; population genetics and its relations to mutation, selection, intermarriage, isolates, assortative mating, genetic drift and differential fertility; anthropological genetics, including problems of parentage and identification, somatology and constitutional types; twin investigations, their methods and results; immuno-genetics, especially blood-group investigations in man; cytological and radiation genetics in man; the identification of carriers of genetic traits; quantitative and multifactor inheritance; lethal and sex-linked genes, phenocopies and experimental pathological genetics; problems of genetic hygiene and genetic counselling.

In 1956 the First International Congress of Human Genetics was held in Copenhagen and was attended by 540 members from all parts of the world, and representing more than 30 countries. An important consequence of the holding of the Conference was the foundation of an international organisation for human genetics. Consideration was given to the reorganisation of «Acta Genetica et Statistica Medica», which hitherto had had a purely

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Scandinavian editorial board, so that this periodical should contribute to the maintenance and development of the unity of purpose in human genetics, particularly in medical genetics, which was created by the Conference.

The Organising Committee of the Congress therefore decided to publish the Proceedings of the Congress in «Acta Genetica et Statistica Medica» as the initial stage in this development. It was also decided to reorganise the journal on an international basis with a number of editors and collaborators representing centres of human genetics all over the world willing to contribute manuscripts and advice.

Only papers written in English, German or French will be accepted for publication. Each paper, whichever language is used, must have a short summary in English. Articles should be as concise as possible; only in special cases will they be allowed to exceed 10 printed pages. Manuscripts should be addressed to the Editorial Secretary, The University Institute of Human Genetics, Tagensvej 14, Copenhagen N., Denmark.

VORWORT

Professor *Gunnar Dahlberg*, der Gründer und Herausgeber der «Acta Genetica et Statistica Medica», ist am 25. Juli 1956 in Uppsala gestorben. Seit der Gründung der Zeitschrift im Jahre 1948 waren *Otto Lous Mohr*, Oslo, und *Tage Kemp*, Kopenhagen, Mitherausgeber. Nach Professor *Dahlbergs* Tod trat *O. L. Mohr* von diesem Amt zurück, so daß *Tage Kemp* als einziger Herausgeber der Zeitschrift zurückblieb.

«Acta Genetica et Statistica Medica» erscheint seit ihrer Gründung im Verlag S. Karger AG., Basel und New York.

In der Einleitung zum ersten Band betonte *Gunnar Dahlberg*, daß die Zeitschrift sich in erster Linie an Mediziner wende, jedoch immer auch den Interessen der Forscher dienen wolle, die sich mit menschlicher Vererbung befassen. Dieser Leitsatz soll auch in Zukunft Gültigkeit behalten. Die Zeitschrift wird weiterhin alle Aspekte der medizinischen Genetik sowie alle Gebiete der menschlichen Vererbungslehre behandeln, die für die medizinische Forschung von Bedeutung sind, und so eine Verbindung zwischen Medizin, Genetik, Demographie und Anthropologie schaffen.

Die Zeitschrift wird sich vor allem der Darstellung und Diskussion folgender Probleme widmen:

Methoden der medizinischen und menschlichen Vererbungslehre einschließlich Demographie und medizinischer Statistik; Populationsgenetik und ihre Beziehungen zur Mutation, Selektion, Verwandtenehen, Isolaten, Paarungssiebung, Gendrift und differentielle Fruchtbarkeit; ferner anthropologische Genetik mit Einschluß der Probleme der Vaterschaftsbestimmung, Somatologie und Konstitutionstypen, Methoden und Ergebnisse der Zwillingsforschung und Immunogenetik, insbesondere Blutgruppenforschung beim Menschen. Außerdem werden Zytogenetik und Strahlen-genetik sowie Probleme der Übertragung krankhafter Erbanlagen durch Gesunde, quantitative und multifaktorielle Vererbung, letale und geschlechtsgebundene Gene, Phänokopien, vergleichende und experimentelle Erbpathologie behandelt werden; schließlich werden auch Erbhygiene und eugenische Beratung Berücksichtigung finden.

Das Redaktionskomitee der «Acta Genetica et Statistica Medica» setzte

sich bisher nur aus Vertretern skandinavischer Länder zusammen. Anlässlich des im Jahre 1956 in Kopenhagen abgehaltenen Ersten Internationalen Kongresses für menschliche Vererbungslehre, der von 540 Teilnehmern aus 30 verschiedenen Ländern besucht war, wurde eine internationale Organisation für menschliche Vererbungsforschung gegründet. Gleichzeitig wurde erwogen, «Acta Genetica et Statistica Medica» zu einem internationalen Organ auszubauen, das der Zusammenarbeit der Forscher aller Länder auf dem Gebiet der menschlichen Vererbung und besonders der medizinischen Genetik, wie sie anlässlich des Ersten Internationalen Kongresses im Jahre 1956 begründet wurde, dienen soll.

Das Organisationskomitee des Kongresses beschloß daher, den Kongreßbericht in «Acta Genetica et Statistica Medica» zu veröffentlichen und damit einen ersten Schritt zur Neugestaltung und Entwicklung der Zeitschrift auf internationaler Basis zu tun. Die neuen Redactores, Editores und Collaboratores aus vielen verschiedenen Ländern der Welt vertreten alle Institute für menschliche Vererbungsforschung, die ihre aktive Mitarbeit zugesagt haben.

Arbeiten können in deutscher, englischer oder französischer Sprache eingereicht werden; jeder Arbeit, gleichgültig in welcher Sprache sie erscheint, soll eine kurze englische Zusammenfassung beigegeben werden. Die Autoren werden gebeten, ihre Arbeiten so kurz wie möglich zu halten. Arbeiten von mehr als 10 Druckseiten werden nur in besonderen Fällen zugelassen. Manuskripte sind an den Redaktions-Sekretär, Universitäts-Institut für menschliche Erblehre, Tagensvej 14, Kopenhagen N, Dänemark, zu senden.

PRÉFACE

Le Professeur *Gunnar Dahlberg*, fondateur et éditeur de «*Acta Genetica et Statistica Medica*» est décédé le 25 juillet 1956 à Upsala. Depuis la fondation de ce périodique, en 1948, *O. L. Mohr*, Oslo, et *Tage Kemp*, Copenhague, en étaient les co-éditeurs. Après la mort du Professeur *Dahlberg*, *O. L. Mohr* se retira, et *Tage Kemp* resta le seul éditeur de la revue.

Dès le début de la parution de «*Acta Genetica et Statistica Medica*» l'édition en a été confiée à la maison *S. Karger A.G.*, Bâle/New York.

Dans l'introduction au premier volume, *Gunnar Dahlberg* avait souligné que cette revue s'adressait en tout premier lieu aux médecins, mais voulait également servir les intérêts de tous les chercheurs qui s'occupent de l'hérédité humaine. Cet objectif doit aussi être poursuivi dans l'avenir. La revue continuera à traiter tous les aspects de la génétique médicale, ainsi que tous les domaines de l'hérédité chez l'homme qui revêtent une importance pour cette science, et veut ainsi créer une liaison entre médecine, génétique, démographie et anthropologie.

La revue sera consacrée avant tout à la présentation et la discussion des problèmes suivants: les méthodes de la génétique médicale et humaine, y compris la démographie et la statistique; la génétique des populations et leurs relations avec les mutations, la sélection, les mariages consanguins, les isolats, les mariages assortis, la dérive génétique et la fertilité différentielle; de plus, la génétique anthropologique – entre autres les problèmes de la recherche de la paternité –, la somatologie et les types constitutionnels, les méthodes et résultats d'études gémellaires et de génétique immunologique, en particulier l'analyse des groupes sanguins. En outre seront traités la cytogénétique et la génétique des radiations, la question de la transmission de facteurs pathologiques par des conducteurs normaux, l'hérédité quantitative et multifactorielle, les gènes létaux et liés au sexe, les phénocopies et la pathologie héréditaire comparée et expérimentale. Enfin, une place sera réservée à la prophylaxie des maladies héréditaires et à l'eugénique.

Le comité de rédaction de «*Acta Genetica et Statistica Medica*» s'était composé jusqu'ici uniquement de représentants de pays scandinaves.

VIII

Lors du Premier Congrès International de Génétique humaine à Copenhague, en 1956, auquel prirent part 540 membres de 30 pays différents, il fut fondé une organisation internationale de génétique humaine. En même temps, il fut envisagé de transformer «Acta Genetica et Statistica Medica» en un organe international, devant favoriser la collaboration des chercheurs de tous les pays dans le domaine de l'hérédité humaine et en particulier de la génétique médicale, ainsi qu'elle a été préconisée lors du Premier Congrès International de Génétique de 1956.

C'est pourquoi le comité d'organisation du Congrès a décidé de publier les rapports de celui-ci dans «Acta Genetica et Statistica Medica» et de faire ainsi le premier pas vers un nouvel essor de cette revue et d'une réorganisation sur une base internationale. Les nouveaux rédacteurs, éditeurs et collaborateurs appartiennent à des pays divers et représentent tous les centres de génétique humaine qui ont accordé leur collaboration active à ce journal.

Tous travaux peuvent être envoyés en langue allemande, anglaise ou française. A chaque article, quelle que soit la langue dans laquelle il est rédigé, doit être joint un bref résumé anglais. Les auteurs sont priés de limiter le plus possible leurs travaux: les manuscrits dépassant 10 pages imprimées ne seront admis que dans des cas exceptionnels. Les travaux sont à adresser au Secrétaire de rédaction, Institut universitaire de Génétique humaine, Tagensvej 14, Copenhague N, Danemark.

PROCEEDINGS OF THE FIRST INTERNATIONAL CONGRESS OF HUMAN GENETICS

Copenhagen, August 1-6, 1956

Edited by

TAGE KEMP

President of the Congress

MOGENS HAUGE

Secretary General

BENT HARVALD

Vice-Secretary General

PART IV



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inside (in brackets): Page-numbers of the Proceedings of the First International Congress of Human Genetics.
outside: Page-numbers of the "Acta Genetica et Statistica Medica".

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innen (in Klammern): Seitenzahlen der Proceedings of the First International Congress of Human Genetics.
außen: Seitenzahlen der «Acta Genetica et Statistica Medica».

Signification des chiffres en haut des pages:

à l'angle interne (entre parenthèses): Numéros des pages des Proceedings of the First International Congress of Human Genetics.
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METHODS IN HUMAN GENETICS

Fisher, R. A.: Acta genet. 7, 7-10, 1957

University of Cambridge, Department of Genetics, Great Britain

METHODS IN HUMAN GENETICS

By R. A. FISHER

The study of heredity in man is carried out by a diversity of methods and for a variety of purposes. Historically, the type of study in man which developed first, or, at least, first deserved the designation of genetics, is the genealogical assembly of human pedigrees of rare or distinctive anomalies. In my own country it is a succession of Scottish ophthalmologists, Nettleship, Usher and Riddell, who have added most to our data in this field. I owe to Professor *W. J. B. Riddell* the information that published pedigrees date back so far as the eighteenth century, when the discovery of anomalies of colour-vision of the type still known as Daltonism were attracting attention.

It is only natural that medically qualified men, having the time, curiosity, and unlimited perseverance needed for such work, were not numerous, and the accumulation of published data certainly was not rapid during the nineteenth century. Still, by the end of that period enough medical pedigrees existed to confirm decisively for the human species, the conclusions as to inheritance, which *Mendel's* own work at that time dramatically rediscovered, and the works of his botanical discoverers had established among plants. It is not clear, and I dare not positively assert, that man was the first member of the animal kingdom to exhibit unmistakably the truth of *Mendel's* discovery, it may have been poultry perhaps, or mice, for their recognition followed rapidly; but it is certain that human material existed at that time ready to be recognized as demonstrating Mendelian inheritance. Indeed, but very little more penetration would have been required to have clarified the inheritance of sex itself, through the occurrence of sex-linked characters, first in the X and later in the Y.

As a consequence of the energetic pursuit of the genealogical method it is probable that many more heritable traits dependent on unit factors are known in mankind than in any other species. These are, however, characteristically rare anomalies of two kinds (a) the so-called autosomal "dominants", which are inherited independently of sex, in that each affected man (or woman) may be expected to transmit his peculiarity to half his sons and to half his daughters. These conditions are indeed never known to be dominant in the sense in which *Mendel* introduced the term, which in this sense implies that the homozygote should be indistinguishable from the heterozygote, which is very likely never the case. What in reality characterizes this group of conditions is that a rare gene should have recognizable effects when heterozygous, so that it is not a true recessive. These recognizable effects are of all kinds, from the slightest peculiarity to the gravest disorder. They are so numerous that many of those recorded must be transmitted on each of the 22 chromosome pairs which are inherited independently of sex. A large proportion must be linked to one or other of the chromosome markers which have come to light in recent years, a circumstance which greatly increases the scientific interest of the establishment of such genealogies.

The second class of factors, which also has appeared rather frequently, is that which is transmitted in the X-segment of the sex-chromosome pair, and in its actual inheritance, while it is transmitted by women impartially to half of their sons and daughters, by men it is to all their daughters, but to none of their sons. It is transmitted to men therefore only from their mothers. Nearly all these X-linked conditions are recessive, so that a woman containing one abnormal gene is phenotypically normal, though she may have a father and sons manifesting the condition. In this class there is included the particularly interesting case of the two kinds of anomaly of colour vision known as Daltonism, or red and green anomaly respectively. These are sufficiently common, one or other affecting perhaps 8% of the men in European populations, that they can serve as chromosome markers in the study of other factors carried in the X or in the pairing segment of the sex chromosome. They are characteristic recessives for though heterozygous females are normal, females homozygous for the same gene show a defect in colour vision similar to that of the males in their families.

The high frequency of defects of colour-vision of these X-linked types, makes them the inevitable basis for the mapping of this portion of the germ plasm. The demonstration by *Waalder* and *Franceschetti* that two distinct loci are involved, shows that there is much more to be learnt of the genetics of the condition. There should be males carrying both mutant genes in the

same chromosome, exhibiting red anomaly with some additional insensitivity and lack of discrimination in the blue-green. There might be so frequent as one in eighteen or so of the red-anomalous, and characterized genealogically by their capacity to be the sires of green-anomalous daughters, if they marry wives carrying the green anomaly. In any case one would like to know the frequency of recombination between the two loci, which could theoretically be determined from the proportion of normal sons occurring in families of women of normal colour vision carrying both defects.

If we rely on the analogy of animals bred for genetic study, the number of recessive peculiarities in man must be even greater than the number of quasi-dominants. These supply no genealogies, but are recognizable by their simultaneous occurrence in whole sibs. A proportion of affected sibs much greater than that of affected parents or offspring is, therefore, an indication of recessive inheritance even when, owing to imperfect manifestation, or to imperfect viability, theoretical *Mendelian* ratios cannot be verified. With rare recessives also valuable confirmation may often be obtained from enquiries as to the consanguinity of the parents, for in British experience only about six marriages in a thousand are between first cousins, so that a much higher proportion in the matings producing rare recessives is conspicuous and can easily be statistically significant. Recessive anomalies, however, unless sex-linked are still among the most elusive which the human geneticist can attempt to elucidate.

A second class of human characteristics offering peculiar difficulties is that of quantitative characters with which must be included defects or anomalies which are too common to allow of effective characterization by pedigree, as in the case of myopia, and which have not been subdivided into classes which are both genetically significant and clinically recognizable. In the history of our subject, on the other hand, the biometrical study of quantitative characters has been of enormous importance through leading to a study of the genetical and biometrical characteristics of a continuing population, so giving an effective insight into the theory of selective improvement, and of Natural Selection. Biometrical methods, with especial emphasis on twin studies, are therefore characteristic of the investigation of quantitative characters.

The fundamental revolution of Human Genetics as a developing science has, however, come in the last few years with the discovery of a considerable series of blood-group systems. It is not my intention on the present occasion, for it would take far too much time, to give an account of this tidal wave of new facts and facilities. Before closing these few remarks, I need only state that owing to the blood groups we are provided with useful

genetic markers not only in the sex chromosome as by Daltonism, but in about one half of the 22 human autosomes also.

The blood-group antigens combine the advantage of distinct recognition to which the rare anomalies owe their value, with the characteristic of comparative commonness in the populations studied, so that almost every family examined is found to segregate in one or more serological characteristics. In the future, pedigree collection should, I believe, always be accompanied by blood-tests covering as many of the serological loci as possible. Moreover we do not know that the rare recessives are not often systematically related to recognizable blood genes, just as these latter have often been found to be related to each other in complex systems involving many loci, certainly four in the MN system, as in that of Rhesus. With the blood groups also must be classed other recognizable traits such as the secretion factor, or the capacity for tasting phenyl-thiocarbamide, which also seem to be maintained in human populations as balanced polymorphisms, and therefore offer the means of elucidating the population structure.

When we consider that nearly all our knowledge of the blood-groups has been acquired since the last war, it is apparent that human genetics so far from being a sluggish or backward science has shown itself to be more dynamic and resourceful perhaps than any other branch of the study of man.

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THE TWIN-STUDY METHOD IN WIDER PERSPECTIVE

By P. J. WAARDENBURG

The origin of the twin method in human genetics dates back to the genius of *Francis Galton* [1875, 1876, afterwards 1883 and 1907]. The aim and scope of *Galton* were, however, not quite congruent with those of modern times. The only thing which *Galton* really knew was the fact that there are two kinds of twins, those originating from a single ovum and those born from two ova.

Galton was unaware of the fact that monovular twins are genetically identical and that only the binovular twins are partly non-identical. His hypothesis that somewhere in the development of the individual a "loss of one half of the total germinal material contributed by the two parents" (stirp) must take place, was an ingenuous conception, but he could not tell at what moment this reduction occurred, because the most fundamental facts of ripening of gametes, fertilisation, inheritance of sex and so on were still unknown. It is very difficult to know *Galton's* conception but I think we are not far wrong when we state that, in his opinion, the *total* heritage of each child of two parents was much alike, also in monovular and in binovular twin partners, but that always a part of the hereditary units remained dormant or latent by the influence of different antenatal circumstances and he speaks of "*an incalculable number of petty accidents that occur to produce variability among brothers*" (with a special calculation for the sisters), so causing the manifest *personal* hereditary differences of siblings. Antenatal circumstances being strongly alike in monovular twins often enveloped in the same foetal membranes *can produce a great degree of similarity* both of manifest and of latent units and therefore of resemblance at birth. For the binovular twins and the other siblings, the antenatal circumstances differed much more, in this way producing a much lesser degree of resemblance at birth. What *Galton* sought to discover was the influence of different postnatal circumstances on twins who were very similar at birth and that of similar circumstances on twins who were rather dissimilar at birth. In Anglosaxon literature it has since been called the nature-nurture problem.

Galton never made a fundamental distinction between monozygotic (MZ) and dizygotic (DZ) twins nor did his first successor *Thorndike* [1905] who investigated psychological traits of twins on a larger scale. Thus, the results of these investigations were rather disappointing.

In the following period, the necessity was felt of differentiating between both groups of twins because in many cases the findings of the placenta and the secundines were lost. *Poll* [1914] sought for a differential method by means of fingerprints. Although each individual has a particular pattern, probably from a polygenic basis, he expected MZ twins to be much more alike than DZ twins, but this investigation did not lead to any practical result.

In 1924, *Siemens* introduced his *polysymptomatic diagnostic method*. Moreover, he laid stress upon the necessity of *comparing representative MZ and DZ twin series* and not to restrict oneself to the MZ twins as before, nor to describe only selected remarkable concordant cases of such twins but

to substitute the casuistical by the statistical method. In this way, an exceptional fortuitous incorrect group diagnosis could do no harm.

It is regrettable that it is in practice often impossible to conform to these demands owing to the limited material available. I am struck by the fact that the many fine unselected studies of hereditary diseases in Denmark and in Sweden have yielded such a small number of valuable twin cases. It is even open to question whether for rare affections international cooperation with the larger countries can afford us material of statistical significance. The most one can do, is to encourage doctors in one's own country to publish their unselected observations in twins to established national centres, so that none are lost. I will give you one striking example. In total we know only of 10 twin cases of retinoblastoma and one in triovular triplets, published from 7 countries (U.S.A., Canada, Austria, England, Sweden, Germany and Switzerland). One unpublished case from the Faeroes came to my knowledge by personal communication. Only 6 cases are with certainty known as MZ, 5 of which are concordant (4 bilaterally, one partner bilaterally in one pair the other unilaterally and one is discordant and unilateral). In one concordant female pair the twin diagnosis is unknown, in another concordant pair sex and twin class are not available. Two DZ pairs of unlike sex are discordant. So the twin cases are here quite inadequate to elucidate the rôle of a germinal mutation and that of a somatic one or another type of phenocopy.

The polysymptomatic class diagnosis

The polysymptomatic class diagnosis was especially welcome since we found that the MZ may be occasionally dichorionic as in the case of which I happen to be the father and which served as a starting point for further investigation of *Siemens. Vouëte* [1935] has established that division before the fourth day of development of the trophoblast gives rise to dichorionic diamniotic MZ twins with their own trophoblast and chorion which are imbedding similarly to DZ twins (± 30 per cent of the cases). In 66 per cent of the cases it takes place between the fourth and seventh day after the imbedding. These twins have separate amnia but they are monochorionic. Splitting between the seventh and the fourteenth day (± 4 per cent, according to *Waterhouse* 10 per cent of the cases) produces 2 primitive streaks covered by one amnion (monochorionic monoamniotic twins). Later incomplete splitting produces conjoined twins or double monsters or slightly localised duplications.

Teratologists tell us nowadays that there may be very rarely MZ double monsters originated from two primitive streaks with a secondary sometimes asymmetrical growing together or "grafting", called *duplicitas cruciata*. Having been charged with the discussion of the twins research method, space will not permit further attention to this topic.

The polysymptomatic method offered little difficulty. We get the impression that the distinction between MZ like sexed twins and DZ partly of like and partly of opposite sex is a real and sufficient one. Only in very rare cases are there difficulties in the twin group diagnosis.

It is, however, desirable especially when the available material is limited to make the twin class diagnosis as reliable as possible and not to advocate the restricted use of local traits or of psychological characters. It is indeed possible sometimes to make an exact diagnosis from dermatological data only (*Siemens* in the beginning) or from eye traits (*Stocks, Jancke* a. o.) or from haematological tests, or from fingerprints combined with palm and sole dermatoglyphics (*Gordon, Allan, Cummins* and *Midlo, Wendt, Ford Walker, Benedikt Nixon* a. o.) or from characteristics of the tympanic membrane (*Lüscher* [1941], who found 13 such traits), or from the behaviour characteristics (*Woltring* [1938]), eventually combined with test drawings (*Woltring* [1938], *Tisserand* et al. [1955]) and so on.

But most authors mentioned felt the necessity of the combination of a great number of qualitatively different traits, that have a full penetrance and are least subjected to gross modifications. In most investigations it is better to omit the twins of opposite sex. *Breiting* [1952] computed that by combination of all haematological tests hitherto known still 4 per cent of like-sexed DZ could be expected as casually concordant. In combination with a number of polygenic physical traits, this concordance of DZ shrinks to a minimum. On the other side, discordance for one hereditary trait is already conclusive for the diagnosis of dizygotism. And, were it not so unpleasant for the twins, a reciprocal skingraft alone would suffice for the diagnosis of monozygotism. The graft is not eliminated in the weeks following the intervention but heals by primary intention (used in a forensic case by *MacIndoe* and *Franceschetti* [1950], and in a very discordant MZ case by *Balavoine* [1954]. Different specificity of graft tissue in DZ could not survive long. To the traits the investigation of which is not expensive or prolonged we count: different details of the iris structure, of the eyebrows, the iris colour and unusual corneal refraction, the ear pattern, facial features, the body height, the implantation of the hair, the structure of the capillaries, the presence or absence of hair at the dorsum of the first and second phalanx of the fingers, etc.

The Comparative Twin Research Method

As for the new comparative twin research method, it has immediately brought various advantages:

I. Restriction to the MZ alone gives:

(a) a preliminary idea of the *range of modifiability* of particular phenotypes (the so-called *stability* or *lability of manifestation*). The postnatal circumstances for the MZ being often more alike than for DZ it may be that this range in reality is somewhat greater than has been found. It does not only apply to quantitative but also to qualitative differences of the MZ partners. So we have learned what clinical pictures do not coexist, e.g. *Kallmann* found never schizophrenia and manic depressive psychosis in one set of MZ, and those which may coexist, e.g. a retinoblastoma with cells of an embryonic type and a retinocytoma with cell rosettes (*Franceschetti*) or unilateral glaucoma simplex without blindness and inflammatory glaucoma, followed by blindness (*Westerlund*), convergent monocular squint with amblyopia and alternating squint without amblyopia (*Waardenburg*) or anencephalus and hydrocephalus (*Bouwens*).

(b) It may elucidate the cause of *decreased penetrance in cases of skipping of generations*. If MZ should occasionally be discordant for some dominant character, the influence of a different genome can be excluded, so that it may only be attributed to dissimilar developmental circumstances. Such instances are MZ females, discordant for colour blindness (*Nettleship* [1912], *Walsh-Matthews* [1952]) or for extraocular nystagmus (*Waardenburg* [1938]) or for congenital luxation of the hip (4 or 6 cases in the literature) or unilaterally discordant for dystosis cleidocranialis (*Liebenam* [1938]), etc. *In these cases change of dominance in heterozygotes* is concerned.

(c) It may give information on the value of different therapeutic methods of nourishment or education, the MZ being, in contrast to *Darlington's* opinion [1953] on vegetative reproduction, the only *isogenic* individuals in man. They have the advantage that they can be compared at the same time and stage of development. This method known as "*twin control testing*" has now also been successfully applied to cattle. A limitation of this method perhaps lies in the fact that what is valid for one set of MZs may not always be valid for all sets or biotypes of MZs.

II. Comparison of both groups of twins may help us to recognize the hereditary basis in all those conditions where family investigation is inadequate:

(a) In solitary cases of a polygenic nature, e.g. in corneal and total refraction, some anthropological traits, etc.

(b) In infantile characters as diatheses, rhachitis, anomalies of the first dentition, etc.

(c) In senile characters as cataract, glaucoma, arteriosclerosis, senile macular dystrophy, etc.

In the period immediately after 1924, the twin study method proved to be a great success and created great enthusiasm. But it has gradually been subjected to *criticism*, which was at first directed against *Siemens's* view, erroneously assumed by his successors that the method would enable us to ascertain quantitatively the relative roles played by heredity and by environment in the development of a phenotype, and to ascertain what characters were caused by circumstances only.

Before applying the twin method we should be well aware of the fact that the *antithesis of hereditary and non-hereditary characters is a theoretical simplification*. It is a matter of practical convenience to call a phenotype or character non-hereditary, when it develops similarly through exogenous circumstances in genetically different individuals and so proves to be rather independent of hereditary tendencies (instances in the physical sphere are: the results of extreme traumata, of poisoning, of serious infections, and in the psychical sphere the results of convention and tradition, the habits, manners and fashions; in both spheres some effects of adaptability and education). It is also wrong to call a distinct phenotype hereditary when it always presents itself in the same way in the most various circumstances. We may then only conclude that the circumstances such as we know are not those which are necessary for the gene to develop. Each gene will remain latent if it does not find its adequate environment. Even for the development of the iris colour, a necessary condition is an intact sympathetic innervation, present in all normal individuals but sometimes defective in an inborn anomaly of the central nervous system or by birth injury and then inhibiting its formation. Now *Siemens* has introduced the term *paratype* for the so-called non-hereditary part of the phenotype as if heredity and environment worked in addition and not in mutual interaction. *Every phenotype, however, is the reaction of the genotype to peristatic and endostatic environmental stimuli*. It is impossible to find the paratype by subtracting the genotype from the phenotype (*Waardenburg* [1927], *Hogben* [1933], *Lenz* [1935], correcting his former standpoint).

Thus the investigators who created methods to estimate the relative forces of hereditary tendencies by similarity or discordance quotients followed erroneous paths which were logically inconsistent with *Johannsen's* conception (*Hug* [1953]). The potential power of the genotype to vary its reactions to different surroundings cannot be measured and the idea that

lability of manifestation (as in the educability and the psychical sphere of man) is less influenced by heredity than is stability (as in the rectilinear instinct sphere of animals) is far from being conclusive. It is only possible to get an impression *which psychical and physical environmental influences are so strong* that the major part of the hereditary differences may be neglected and *which hereditary tendencies have a smaller or larger range of modification under the ordinary circumstances.*

Lenz [1941, 1948] has insisted upon the fact that our calculation of the power of heredity by the method of establishing correlation coefficients and by the twin method are partly contradictory. They are influenced by local circumstances and gene frequencies in the population and by other factors. The sound criticism which he utters in diverse articles has, to my mind, not been given sufficient attention.

The twin research method shows indeed several limitations and shortcomings:

(a) MZ twins often develop under extraordinary circumstances and their discordancies may occasionally increase to such an extent that their modifications largely surpass the normal range of modification. This tendency to maldevelopment in one of the MZ partners is, however advantageous in the study of embryological development and of twinning in general.

For an exact scientific interpretation of the phenotypical facts *we badly need a clearer definition of the conception of the environment* with which the gene cooperates, especially of the endostatic environment in fecundation and in embryological development. We have to envisage firstly, the microstructure pattern of the cytoplasm of the egg cell eventually transformed by the sperm after fecundation, secondly, the rate of embryological development and differentiation in general and that in both body halves and in twin formation in particular, and thirdly, the epistatic and inhibitive influences of the rest of the genome. It is only by better definition of these environmental influences that we can answer the question whether we inevitably need assumptions like that of *Dahlberg's* genotypical asymetry, of *Lenz's* genes with developmental lability and of *von Verschuer's* autonomic mode of reaction of genes. Of these, that of *Lenz* appears the most attractive to me personally.

As I see it, we are obviously often wrong when we, neglecting *Galton's* petty accidents and other influences still unknown to us, proclaim the similarity of developmental circumstances in twins and therefore look for a peculiar behaviour of the gene.

Differences between MZ partners may be due to special circulatory and other circumstances before birth, so that it becomes very difficult to recognize and value the pre- or postnatal causes of such differences, especially when they are rather large. This handicap is also present when estimating occasional discordances of MZ reared apart.

Discordances of MZ moreover largely depend upon the age and the period of observation. We therefore highly appreciate that *von Verschuer* and his assistants are again investigating their twins after an interval of 25 years in order to get insight into modifying influences on their phenotypes. In this way, they are making a kind of longitudinal section of life to complete the former transverse section.

(b) The increased mirror imaging (lateral inversion) in MZ twins is a handicap for settling whatever variations of the normal asymmetry such as lefthandedness or situs inversus viscerum may have hereditary tendencies of their own. The asymmetry problem as a whole with all its consequences is involved in the study of twinning.

According to *Keeler* [1929] it is well established that gross internal mirrorings in double monsters are more frequent than in identical twins. External reversions have been studied by him on a series of 10 double monsters which he compared with 14 pairs of MZ, all showing asymmetries.

Some mirroring was found in 29 per cent of the MZ, in 33 per cent of the monsters joined centrally and in 66 per cent of the monsters joined laterally. It was thought that relative *position, orientation and time of separation* may be factors involved in determining reversals. To *Newman* [1928, 1940] mirror imaging is important confirmatory evidence of monozygotism especially in the less similar pairs. One thing is certain: that the various external and internal traits (e.g. handedness, situs inversus) are quite independent of each other and so are rarely found combined. Moreover, situs inversus is not at all typical for MZ. The literature contains only a few cases. *Kean's* case [1942] of concordant situs inversus in female MZ is unique.

(d) The amount of discordances for hereditary traits of DZ twins depends upon the heterogenesis of the population and of that of the parents of the twins.

(c) The modification range of MZ and DZ is often dependant upon the casual variability of circumstances in the population.

(f) Methodical failures of measurements do increase the apparent discordance of MZ and decrease that of DZ especially when the real differences are small, as is usually the case in MZ.

(g) The environment for MZ partners and for DZ partners is not similar

as is so often supposed. Before birth it may be much more different for MZ and after birth much more alike for MZ than for DZ. Individuals choose and produce their own surroundings, especially concerning the psychological sphere, to a great extent themselves as a result of their hereditary tendencies. This is also true for athletic and artistic dispositions.

(h) Concordance and discordance have not the same significance in MZ and in DZ. The result of measuring is very much dependant upon the standard used, especially in continuously varying and in psychological characters. A finer graduation increases the discordance of DZ, a rougher graduation increases the concordance of DZ as well as of MZ without this being real.

Even the mode of inheritance and the heterozygous and homozygous state have a different influence on the concordance or discordance of DZ and of MZ (*Dahlberg* [1942] a.o.). So degrees of similarity and other attributes are often compared which are incomparable.

Notwithstanding all these objections the comparative twin method has offered many valuable results in different fields of human pathology, a part of which Prof. *von Verschuer* will illustrate. *We have obtained much useful information about phenotypical plasticity and stability.*

Does a Third Type of Twins Exist?

Although the polysymptomatic method seldom gives difficulties and we may neglect a wrong class group diagnostic in a statistically unobjectionable material, it is the *occasional difficulty* mentioned that has given rise with other disputed facts (influence of the father, occurrence of MZ and DZ twins in multiple births, increase of MZ twinning in kindreds with probably inherited DZ twinning), to the assumption of a third type of twins. This type was supposed to be alike in its maternally inherited traits because it was thought, in correspondance with facts known in animals, that a large second polar body, originated by equational cleavage was fecundated, whereas the parental inheritance from two sperms was obviously different.

The second polar body is formed after entrance of the sperm into the ovum and so may be influenced by the father. Unfortunately cyto- and karyology do not give much support to this event because in mammals and man the second division seems to be the reduction division. Moreover, the process is rather complicated by crossing over so that prereduction and postreduction do not remain quite opposite to each other. Thus, for some chromosome parts prereduction may be valid whereas for the remainder

postreduction is the more common situation. Each allelic pair of genes has its own frequency of pre- and postreduction which is dependant upon its locus in the chromosome. These frequencies may vary from 0 to 100 per cent.

I do not think it is necessary to dwell on this problem because the cases we are unable to decide to which twin groups they belong are so rare that we do not much need an answer to the question whether there is still a third group of twins.

It is of no consequences for the twin method hitherto used. Moreover, it is extremely difficult to obtain conclusive evidence for its existence, because large numbers of dominant maternal traits are needed to obtain significant statistical results.

Thus, I approach my *last important question* in connection with the twin method.

Do we agree with *Bronson Price's* assumption [1950] that intrapair differences are greater in monochorial than in dichorial MZ cases? Should we follow his advice in future and separate both types, which implies a scrupulous research into the condition of the foetal membranes and the placenta to get an answer to the question whether in special cases the MZ differences are due to antenatal influences? For the study of postnatal influences he namely advocates the investigation of dichorial MZ twins, whereas the study of the prenatal influences and the solving of problems of developmental genetics may be advanced by examination of monochorial MZ. Is it not a little embarrassing that dichorial MZ may also show occasionally lateral inversions, as found by myself and by *Voûte* (dental and scapular anomalies and squinting). It suggests that already the cleavage as such may in some cases produce the reversal.

In connection with the different results of the time of separation, the question arises whether this time is quite accidental and so is an art of modification. We do not know as yet in how many cases the twinning tendency is a hereditary trait and how it is with MZs and its various types. Is it only a casual coincidence that *Voûte* has mentioned two cases of dichoriatic MZ among children of a brother and a sister and that *Bruins* [1953 and 1955] reports on a familial late cleavage in a case of an acardiac and of a dicephalous, and that he found spina bifida, hydrocephalus and other connatal anomalies in the same pedigree? He also mentions an acardiac with an anencephalic twin partner. This case shows affinity to an interesting case of *Bouwens* [1954] where one of monochorial monamniotic MZ partners showed anencephaly with vertebral block formation and the other slight hydrocephaly with *Klippel-Feil* and spina bifida aperta inferior.

Bouwens's case was probably the result of a homozygous combination of inherited status dysraphicus present in both parents and in several family members, and it shows as in the cases of *Bruins* how MZ partners sometimes may differ and how *necessary it is not only to restrict ourselves to the study of twins only, but to combine it with research of the whole family.*

No qualified investigator will pretend that the twin study method is omnipotent. The various methods used in human heredity must supplement one another. It is therefore that I can not fully admit that the similarity method is a *petitio principii*, based upon a circular way of reasoning and for this reason objectionable. Should the twin study method have its limitation "this should not prevent its widest use in those many fields where it is applicable" (*Kallmann* [1954]).

For those who are so critically minded that they no longer appreciate the twin study method, the excellent work of *von Verschuer*, *Kallmann* and their school a.o. has been carried out and the splendid comprehensive book by *Gedda* has been written in vain.

Discussion

E. T. O. Slater (London): Dr. *Waardenburg* has drawn attention to sources of difficulty in the application of the twin method. These difficulties have recently been strongly emphasized by Prof. *Neel* and Dr. *Schull* in their well-known textbook ("Human Heredity", Chicago 1954). The verdict of these authorities is, indeed, crushing. (The speaker gave a quotation.) Now if the field worker concerned with the genetical aspects of common and obscure disorders were deprived of the tool available in the twin method he would be left poor indeed. Science has to use the simpler for the elucidation of the more complex. Our knowledge of the biology of twins is better founded, more objective and more precise than our knowledge of, say, schizophrenia. The field worker will continue to have to use twins for the elucidation of such problems, even if he cannot attain the standards, e.g. in the determination of zygosity, required by workers on the biology of twinning for their own studies. The "handicaps" of Dr. *Waardenburg*, the "biases" of Prof. *Neel* are surely unavoidable natural complexities. Their possibly disturbing effect is a matter to be taken into account in the framework of each individual field research. Their mere existence should not be regarded as adequate grounds for the rejection of results attained by work on twins, until evidence can be produced that those results have actually been distorted and made misleading.

J. V. Neel (Ann Arbor, Michigan): One might infer from Dr. *Slater's* remarks that Dr. *Schull* and I had little use for the twin method in genetic research. This is most emphatically not the case. We regard it as one of the most powerful tools that we as human geneticists possess. But we were concerned at the time we wrote the book—and are still concerned—with a number of important biases in the twin method which are not sufficiently appreciated by the average worker. So far as I am concerned, the remarks of the several speakers on this program, emphasizing as they did many of the problems of the twin method, constitute a sufficient justification of our position.

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ÜBER DEN METHODISCHEN BEITRAG DER ZWILLINGSFORSCHUNG FÜR DIE HUMANGENETIK

Von O. Frhr. v. VERSCHUER

Eineiige Zwillinge sind erbgleiche Menschen, zweieiige Zwillinge sind gewöhnliche Geschwister, nur gleichen Alters. Diese grundlegende Regel der Zwillingsforschung hat durch die Erfahrung ihre Bestätigung gefunden. Ausnahmen kommen, wenn überhaupt, nur selten vor. Sie können nur für den einzelnen Fall Bedeutung haben, nicht aber für den statistischen Vergleich zwischen Zwillingsgruppen.

Als eine zuverlässige Methode zur Unterscheidung zwischen ein- und zweieiigen Zwillingen unter den Zwillingen gleichen Geschlechts gefunden war, konnte vor mehr als dreißig Jahren mit der eigentlichen Zwillingsforschung begonnen werden. Sie bestand zunächst in der Sammlung von Zwillingsbeobachtungen, wie sie für den Forscher gerade erreichbar waren. Bald erkannte man jedoch die Notwendigkeit, nur auslesefreie Serien miteinander zu vergleichen. Daß bei der Deutung der Befunde zahlreiche Gesichtspunkte eine große Rolle spielen, haben wir soeben in dem Referat von Herrn *Waardenburg* gehört. Eine Gruppierung der Zwillingspaare nicht nur nach ein- und zweieiigen Zwillingen, sondern auch nach den Umweltverhältnissen ist ein besonders wichtiger Ansatz für die biologische Analyse.

Betrachten wir zunächst die Zwillingsbefunde bei einem zweifellos erblichen Merkmal, den Blutgruppen des ABO-Systems (Tabelle 1). Wir finden eine ausnahmslose Konkordanz der eineiigen Zwillinge, während bei den zweieiigen der Konkordanzprozentsatz sehr deutlich von der Häufigkeit des Merkmals abhängig ist.

Ein ganz anderer Befund zeigt sich bei einem vorwiegend umweltbedingten Merkmal, dem *endemischen Kropf* [1]. Der Vergleich zwischen ein- und zweieiigen Zwillingen mit gleicher Umwelt ergibt in beiden Grup-

Tabelle 1. Die Blutgruppen bei ein- und zweieiigen Zwillingen (v. Verschuer [1934])

	EZ			ZZ			Konkordanz in % EZ:ZZ	Häufigkeit der betr. Blutgruppe in %
	n	k	d	n	k	d		
Blutgruppe O	176	176	—	803	402	401	100:50	50
Blutgruppe A	188	188	—	584	244	340	100:42	37
Blutgruppe B	57	57	—	170	38	132	100:22	10
Blutgruppe AB	22	22	—	59	8	51	100:14	3

Erläuterung: EZ = eineiige Zwillinge, ZZ = zweieiige Zwillinge, n = Anzahl der Zwillingspaare, k = konkordant, d = diskordant.

pen die gleiche Konkordanzhäufigkeit von rund 70 %. Das Überwiegen der exogenen Faktoren bei der Entstehung des endemischen Kropfes zeigen die hinsichtlich der Umwelt diskordanten eineiigen Paare, bei welchen der Konkordanzsatz für den Kropf auf 24 % sinkt (Tabelle 2). Eine erbliche Strumaanlage läßt sich somit nicht nachweisen und doch ist eine unspezifische Erbveranlagung dadurch erkennbar, daß Form und Lokalisation des Kropfes und die Art des Krankheitsverlaufs bei den konkordanten EZ viel ähnlicher als bei den konkordanten ZZ sind.

Tabelle 2. Endemischer Kropf bei Zwillingen (Eugster)

EZ	Umwelt gleich	Konkordanz	71 %
EZ	Umwelt verschieden	α	24 %
ZZ	Umwelt gleich	α	70 %

Sehr aufschlußreich sind Zwillingsbeobachtungen bei pathologischen Merkmalen, die angeboren sind oder sich in frühem Alter manifestieren. Als geeignete Beispiele erwähne ich hier die Serienbeobachtungen über *Hüftluxation* und *Klumpfuß* [2, 3] (Tabelle 3). Der große Unterschied in der Konkordanzhäufigkeit bei ein- und zweieiigen Zwillingen beweist die Erbgrundlage für beide Anomalien: Eine Störung in dem Vorgang der Verknöcherung von Becken und Unterschenkel bei der Hüftluxation und eine Fehlanlage im unteren Teil des Rückenmarks (Myelodysplasie) beim Klumpfuß. Die früher als ursächlich angeschuldigten exogenen Faktoren konnten durch genauere Analyse der Zwillingsbeobachtungen entweder als unerheblich oder nur als mitwirkende Einflüsse bei vorhandener Erbveranlagung nachgewiesen werden. Bei der Hüftluxation zeigt sich eine gute Übereinstimmung zwischen der Konkordanz der EZ und der Konkordanz der beiden

Tabelle 3. Konkordante Zwillingspaare in den auslesefreien Serien von *Idelberger*

	Erbgleiche Paare			Allg. Häufigkeit der Doppelseitigkeit des Leidens	Erbverschiedene Paare			Häufigkeit des Leidens unter den Geschwistern der Kranken
	Anzahl	davon konkordant abs.	in %		Anzahl	davon konkordant abs.	in %	
Hüftluxation	29	12	41,4	41 %	109	3	2,8	2,8 %
Klumpfuß	35	8	22,9	55 %	133	3	2,3	ca. 3 %

Körperhälften, während bei dem Klumpfuß sich die krankhafte Störung auf den beiden Körperseiten gleichmäßiger als bei der Hüftluxation auswirkt. Es zeigt sich bei beiden Leiden eine gute Übereinstimmung in der Häufigkeit der Konkordanz bei zweieiigen Zwillingen und der Häufigkeit des Leidens unter den Geschwistern der Kranken. Bei bilateral symmetrischen Merkmalen ist somit die Heranziehung der beiden Körperseiten zum Vergleich mit den EZ-Befunden fruchtbar. Auch der Vergleich zwischen zweieiigen Zwillingen und Nichtzwillings-Geschwisterpaaren ist wertvoll. Das Beispiel zeigt, daß zur Absicherung der Befunde stets Ergebnisse aus anderen Forschungen mit herangezogen werden müssen, insbesondere der Familienforschung.

Bei der Hüftluxation und dem Klumpfuß handelt es sich keineswegs um erbliche Anomalien mit einem regelmäßigen Erbgang. Die Tatsache, daß unter den erbgleichen Zwillingspaaren bei der Hüftluxation nur zwei Fünftel der Paare und beim Klumpfuß gar nur ein Viertel der Paare konkordant sind, beweist, daß es sich in beiden Fällen um sogenannte schwache Gene handelt, das heißt um Erbanlagen, die nur in einem Teil der Fälle in Erscheinung treten. Ob solch ein pathologisches Gen sich manifestiert oder nicht, hängt also noch von anderen Faktoren ab. So ist z. B. von ganz unterschiedlicher Bedeutung bei den beiden Anomalien die Geschlechtskonstitution, indem die pathologische Anlage für Hüftluxation im weiblichen Geschlecht fünf- bis sechsmal häufiger als beim männlichen Geschlecht in Erscheinung tritt, oder anders ausgedrückt: beim männlichen Geschlecht fünf- bis sechsmal häufiger als beim weiblichen Geschlecht latent bleibt. Beim Klumpfuß dagegen tritt die krankhafte Anlage im männlichen Geschlecht doppelt so häufig in Erscheinung wie beim weiblichen Geschlecht.

Besonders aufschlußreich sind Zwillingsbeobachtungen bei Krankheiten, die erst während des nachgeburtlichen Lebens auftreten, von erblichen und nichterblichen Einflüssen abhängig sind, und bei welchen wegen ihrer Häufigkeit und anderer Komplikationen eine genetische Analyse mit Hilfe der Familienforschung zu keinem befriedigenden Ergebnis führt.

Geeignete Beispiele für diesen Teil der Zwillingsforschung sind die *Tuberkulose* und der *Krebs*. Tabelle 4 gibt eine Zusammenfassung aller bisherigen Serienbeobachtungen [7]. Daraus geht klar hervor, daß bei der Tuberkulose der Unterschied in der Konkordanzhäufigkeit zwischen EZ (74 %) und ZZ (28 %) so groß ist, daß die Annahme einer spezifischen Erbdisposition für Tuberkulose zwingend erscheint. Bei dem Krebs [8] hingegen ist die Konkordanzhäufigkeit bei den eineiigen Zwillingen (21 %) nur gering höher als bei den zweieiigen Zwillingen (15 %). Der Unterschied ist nicht gesichert, wenn man berücksichtigt, daß bei einigen der Zwillingsserien konkordante eineiige Zwillinge häufiger erfaßt wurden. So ergeben die Zwillingsuntersuchungen beim Krebs im Gegensatz zur Tuberkulose keine spezifische Erbdisposition. Betrachten wir jedoch (Tabelle 5) die konkordanten Zwillingspaare genauer, indem wir zwischen den beiden Gruppen unterscheiden:

Tabelle 4. Konkordante Zwillingspaare (nur Serienbeobachtungen)

	Anzahl	Erbgleiche Paare		Anzahl	Erbverschiedene Paare	
		davon konkordant abs.	in %		davon konkordant abs.	in %
Tuberkulose	190	141	74	427	121	28
Krebs	120	25	21	287	44	15

Tabelle 5. Alle Zwillingsserien mit Krebs (Stand von 1956)

	n	Eineiige Zwillinge			n	Zweieiige Zwillinge		
		kk	kd	d		kk	kd	d
	120	20	5	95	287	7	37	243
Konkordanz: Diskordanz		= 25	:	95		44	:	243
in Prozenten		= 21	:	79		15	:	85

1. beide Paarlinge denselben Krebs gleicher Lokalisation (kk), 2. verschiedene Art und Lokalisation des Krebses bei den Paarlingen (kd), so haben wir bei den eineiigen Zwillingen ein Verhältnis von kk:kd wie 20:5, bei den zweieiigen Zwillingen hingegen wie 7:37. Der Erbeinfluß zeigt sich somit beim Krebs nicht in bezug auf die Erkrankung selbst, sondern in bezug auf die Lokalisation und Art des Krebses. Wie die nächste Übersicht erkennen läßt (Tabelle 6), verhalten sich die einzelnen Krebsformen dabei wahrscheinlich verschieden: Beim Magenkrebs ist die Kon-

Tabelle 6. Einzelne Krebsformen (nur die Zwillingsserien von v. Verschuer und Kober; Habs; Busk, Clemmesen und Nielsen)

	n	Eineiige Zwillinge			n	Zweieiige Zwillinge		
		kk	kd	d		kk	kd	d
Magenkrebs	11	3	1	7	24	1	6	17
Brustkrebs	18	1	—	17	37	1	4	32
Gebärmutterkrebs	16	1	—	15	21	—	4	17

kordanz größer als beim Mamma- und Uteruskarzinom, doch müssen noch weitere Beobachtungen abgewartet werden.

Bei einer Krankheit, die sich über Jahre und Jahrzehnte des Lebens erstrecken kann, ist der Querschnitt durch eine Zwillingsgruppe keine ausreichende Unterlage. Eine *Längsschnitts*betrachtung ist notwendig, d. h. die Zwillingspaare müssen durch ihr weiteres Leben hindurch unter Beobachtung gehalten werden. Über zwei solche Untersuchungen bei Tuberkulose und Krebs sei hier kurz berichtet. Tabelle 7 gibt das Ergebnis einer Nachuntersuchung bei den von *Diehl* und mir zuletzt 1935 veröffentlichten und von *Mitschrich* [5] im Jahre 1955 nachuntersuchten Beobachtungen an tuberkulösen Zwillingen wieder. Seit der Ersterkrankung sind somit mindestens zwanzig Jahre, meist noch mehr, vergangen. Wir betrachten die Zwillingspaare, erbverschiedene und erbgleiche jeweils getrennt, in den beiden großen Gruppen: I. Zwillingspaare mit tuberkulösen Veränderungen nur bei *einem* Paarling und II. Zwillingspaare mit tuberkulösen Veränderungen bei *beiden* Paarlingen. Bei der letzteren Gruppe wurde eine Aufteilung in a) Tuberkulosefrühformen und b) Tuberkulosespätformen vorgenommen. Ausgang für diese Gruppeneinteilung war der Befund im Jahre 1935. Die Tabelle gibt in der ersten Spalte die Anzahl der Zwillingspaare für jede dieser Gruppen an. Die folgenden Spalten berichten über den Ausgang der Tuberkulose, und zwar jeweils getrennt für 1. den früher kranken (Gruppe I) bzw. schwerer kranken Paarling (Gruppe II) und 2. den früher gesunden (Gruppe I) bzw. leichter kranken Paarling (Gruppe II). Aus der Tabelle ist zu entnehmen, wie häufig die Tuberkulose zum Tode geführt hat, bei der Nachuntersuchung noch fort dauerte oder in Ausheilung übergegangen ist. Die geringe Besetzung der mittleren Spalte (noch tuberkulosekrank) beweist, daß die damaligen tuberkulösen Erkrankungen weitgehend zum Abschluß gekommen sind.

Was nun zunächst die Gruppe der Zwillingspaare mit tuberkulösen Veränderungen nur bei *einem* Paarling (tuberkulosediskordante Paare) be-

Tabelle 7

Befund 1935	Anzahl	Befund bei der Nachuntersuchung					
		Der früher kranke bzw. schwerer kranke Paarling			Der früher gesunde bzw. leichter kranke Paarling		
		† an Tbc	noch tbc-krank	tbc-gesund	† an Tbc	noch tbc-krank	tbc-gesund
<hr/>							
I. Tuberkulose nur bei einem Paarling							
1. Erbverschiedene Paare	34	19	5	10	1	—	33
2. Erbgleiche Paare	11	1	1	9	1	—	10
II. Tuberkulose bei beiden Paarlingen							
a) Tuberkulose-Frühformen							
1. Erbverschiedene Paare	10	—	1	9	—	—	10
2. Erbgleiche Paare	14	2 *	—	12	—	—	14
b) Tuberkulose-Spätformen							
1. Erbverschiedene Paare	18	14	—	4	—	1	17
2. Erbgleiche Paare	15	10	1	4	4	1	10

* schon damals

trifft, so zeigt sich ein eindrucksvoller Unterschied zwischen ein- und zweieiigen Zwillingen: Während bei den 34 erbverschiedenen Paaren 19mal der kranke Paarling an Tuberkulose gestorben ist, trat solch ein Ereignis bei den 11 erbgleichen Paaren nur einmal auf. In diesem einen Fall von eineiigen Zwillingen erkrankte jedoch auch der andere Paarling, und beide Paarlinge sind an Tuberkulose gestorben. Der einzige Fall der 34 zweieiigen Paare, bei welchen der früher gesunde Paarling in der Zwischenzeit an Tuberkulose gestorben ist, betrifft jedoch ein Paar, bei welchem der damals kranke Paarling wieder gesund geworden ist, so daß bei den erbverschiedenen Paaren in keinem Fall ein Nachziehen des anderen Paarlings in den Tuberkulosestod des einen festgestellt werden konnte. Besonders auffällig ist auch das häufige Gesundwerden der erkrankten Zwillinge bei den tuberkulosediskordanten erbgleichen Paaren. Wie schon früher festgestellt (Diehl und v. Verschuier), ist das dauernde Gesundbleiben des einen Paarlings von EZ ein Indizium für eine relativ gute Resistenz gegenüber der Tuberkulose; ihr zufolge überwindet der erkrankte Paarling häufig seine Krankheit.

Über die Tuberkulose-Frühformen ist lediglich zu sagen, daß sowohl bei den eineiigen als auch bei den zweieiigen Paaren nach Ausheilung der

kindlichen Tuberkulose meist keine erneute tuberkulöse Erkrankung mehr aufgetreten ist.

Ein deutlicher Unterschied zwischen ein- und zweieiigen Zwillingen zeigt sich wieder bei den Zwillingspaaren mit Tuberkulose-Spätformen bei *beiden* Paarlingen: Während bei den 18 erbverschiedenen Zwillingspaaren dieser Gruppe keinmal der leichter kranke Paarling seinem an Tuberkulose verstorbenen Zwillingsbruder oder seiner Zwillingschwester im Tode gefolgt ist, hat bei den 10 eineiigen Paaren, bei welchen der schwerer kranke Paarling seinem Leiden erlegen ist, viermal das gleiche Schicksal auch den ursprünglich leichter erkrankten Paarling ereilt. Insgesamt trat bei der Gesamtzwillingsgruppe der Tuberkulose-tod beider Paarlinge bei 8 eineiigen Zwillingspaaren ein. Die durchschnittliche Differenz des Todesalters dieser 8 Paare war 8 Jahre, 9 Monate, das heißt: neben einigen Paaren mit rasch hintereinander erfolgtem Tuberkulose-tod finden sich andere mit erheblicher zeitlicher Differenz (bis zu 18 Jahren).

Aus Tabelle 8 geht hervor, daß unter den Zwillingspaaren mit tuberkulösen Veränderungen bei beiden Paarlingen der Tuberkulose-tod beider Paarlinge nur bei den erbgleichen Paaren (fünfmal), keinmal bei den erbverschiedenen Paaren eingetreten ist. Daß der Tod des einen Paarlings von eineiigen Paaren nicht unbedingt den Tod des anderen nach sich ziehen muß, erkennen wir aus der Tatsache, daß bei 6 eineiigen Paaren – trotz des Todes des einen Paarlings – der andere seine Tuberkulose überwunden hat. Bei den zweieiigen Zwillingen mit tuberkulösen Veränderungen bei beiden Paarlingen ist der Tod des einen und das Gesundwerden des anderen der Regelfall (bei 16 unter 21 Paaren eingetreten).

Tabelle 8. Zwillingspaare mit tuberkulösen Veränderungen

	bei beiden Paarlingen			bei einem Paarling	
	Beide Paarlinge †	Beide Paarlinge klinisch gesund	Ein Paarling †, der andere klinisch gesund	Der Paarling †	Der Paarling klinisch gesund
Erbgleiche Paare	5	8	6	—	5
Erbverschiedene Paare	—	4	16	17	11

Unter den Zwillingspaaren mit tuberkulösen Veränderungen nur bei *einem* Paarling fällt besonders auf, daß der Tuberkulose-tod des erkrankten Paarlings unter den eineiigen Zwillingen keinmal, unter den zweieiigen Zwillingen dagegen 17mal eingetreten ist.

Die Ergebnisse dieser Forschung in bezug auf die Tuberkulose können hier nicht näher besprochen werden. Deutlich wird jedoch, daß die Ergebnisse der ersten Querschnittsuntersuchungen eine wichtige Bestätigung erfahren haben. Die erbliche Veranlagung ist auch für den *Verlauf* und den *Ausgang* einer einmal aufgetretenen tuberkulösen Erkrankung – neben zahlreichen exogenen Faktoren – von Bedeutung.

Die zweite Längsschnittsuntersuchung bezieht sich auf den Krebs [8]. Auf Tabelle 9 sind die Befunde der ersten und der letzten Untersuchung einander gegenübergestellt. Es wurden Zwillinge, die in den Jahren 1933 bis 1938 an Krebs erkrankt waren, erfaßt. Die Beobachtungszeit erstreckt sich somit auf rund zwanzig Jahre. Schon bei der ersten Untersuchung fiel die überwiegende Diskordanz der eineiigen Zwillinge (21 von 23) auf. Die Annahme, daß im Laufe der weiteren Beobachtung die damals diskordanten Paare konkordant werden könnten, hat sich nur in einem Fall verwirklicht, was die allgemeine Erwartung für das inzwischen erreichte höhere Alter sicher nicht übertrifft. Von den 49 damals diskordanten zweieiigen Paaren sind 5 konkordant geworden, also sicher nicht weniger als bei den EZ.

Tabelle 9. Zwillinge mit Krebs (v. Verschuer und Kober)

	n	Eineiige Zwillinge				Zweieiige Zwillinge		
		kk	kd	d	n	kk	kd	d
1940	23	2	—	21	56	1	6	49
1956	26	3	—	23 (20)	64	2	10	52 (42)
Konkordanz:								
Diskordanz	=	3	:	20		12	:	42

War anfänglich die hohe Konkordanz bei eineiigen Zwillingspaaren – ihr gleichzeitiges Erkranken an demselben Krebs – das auffälligste Ereignis, so müssen wir heute gerade umgekehrt das Diskordantbleiben von eineiigen Zwillingen als besonders bemerkenswerte Tatsache hervorheben: Woher kommt es, daß von erbgleichen Menschen, auch wenn sie zusammen leben und unter offenbar gleichen Umweltbedingungen stehen, nur der eine an Krebs erkrankt und vielleicht daran stirbt, während der andere gesund bleibt und ein hohes Alter erreichen kann, ohne an Krebs zu erkranken? Auf diese Frage kann heute noch keine befriedigende Antwort gegeben werden.

Es ist notwendig, daß wir unsere Längsschnittsuntersuchungen auf das Auftreten von Krankheiten im Leben der Zwillinge ganz allgemein ausdehnen.

Ich kann hier über die Befunde an zwei Zwillingsserien berichten [4, 6], die beide jeweils rund 25 Jahre unter Beobachtung gestanden haben (Tabelle 10). Die eine Zwillingsserie stammt aus Württemberg, die andere aus Berlin. Der Tabelle ist zu entnehmen, wie häufig während diesen 25 Jahren schwere, lebensbedrohliche Krankheiten bei ein- und zweieiigen Zwillingen konkordant oder diskordant aufgetreten sind. Es wurden vorher alle diejenigen Krankheitsfälle ausgeschieden, bei welchen eine klare Kausalbeziehung zu pathogenen Umweltfaktoren (z. B. Typhus, Malaria, Gelbsucht) oder krankhaften Erbanlagen (z. B. Diabetes, Schizophrenie) anzunehmen waren.

Tabelle 10. Auftreten von schweren, lebensbedrohlichen Krankheiten (nach Ausscheiden der Fälle mit klarer Kausalbeziehung zu Umweltfaktoren oder krankhaften Erbanlagen)

	EZ		ZZ	
	k	d	k	d
100 EZ und 50 ZZ aus Württemberg (<i>v. Vershuer</i>) in der Zeit zwischen 1924 und 1950	6	45	1	16
113 EZ und 108 ZZ aus Berlin (<i>G. Koch</i>) in der Zeit zwischen 1928 und 1956	16	23	4	33

Bei der württembergischen Gruppe ist die vorwiegende Diskordanz das auffällige Ereignis, während bei der Berliner Gruppe konkordante Erkrankung häufiger zu verzeichnen war, was wohl damit zusammenhängen dürfte, daß die Berliner Zwillinge in der Berichtszeit (Kriegs- und Nachkriegszeit) unter schwersten äußerlichen Belastungen leben mußten, während die Zwillinge in Württemberg den Kriegseinwirkungen nicht so stark ausgesetzt waren. Aber auch hier bleibt die Frage: Warum wird von eineiigen Zwillingen, auch wenn sie in gleicher Umwelt leben, nur der eine von einer schweren Krankheit befallen, der andere nicht? Die Untersuchung der Umweltverhältnisse hat bei unseren Untersuchungen zu keiner befriedigenden Antwort geführt. Weitere Forschungen sind notwendig.

Die angeführten Beispiele mögen genügen, um den methodischen Beitrag der Zwillingsforschung für die Humangenetik zur Darstellung zu bringen. Wurde früher die Zwillingsforschung als Methode der genetischen

Entwicklungsphysiologie bezeichnet, so dürfen wir heute erweiternd feststellen: Sie ist eine einzigartige Methode der Biologie und Pathologie des Menschen. Die genetische Fragestellung, die am Anfang im Vordergrund stand, hat eine Erweiterung gefunden durch die Fragen nach der Bedeutung der Umwelt für den Menschen, die sich nirgends so klar erfassen läßt wie durch die Beobachtung von eineiigen Zwillingen. Die Zwillingsforschung ist in erster Linie eine biologische Methode. Sie hat es aber immer mit dem *ganzen* Menschen zu tun. Wir werden damit durch sie auch vor weitergreifende Probleme unseres menschlichen Seins gestellt, die zu erörtern den Rahmen dieses Referates sprengen würde.

Die Zwillingsforschung hat sich aus der anfänglichen Sammlung von Zwillingsbeobachtungen zur Querschnittsuntersuchung an auslesefreien Serien und den dazugehörigen Familien (*Kallmann*) schließlich zur Längsschnittsbetrachtung der Lebensabläufe von Zwillingsgruppen entfaltet. Es bedarf keiner Betonung, daß derartige Forschungen nicht mehr ad hoc von einzelnen Forschern unternommen werden können: doch sei betont, daß sorgfältig durchgearbeitete Einzelbeobachtungen auch heute noch von großem Wert sein können. Wir brauchen Zwillingsarchive in den Instituten für Humangenetik, in welchen die Beobachtungen gesammelt und durch Nachuntersuchungen immer wieder ergänzt werden. Wir dürfen von dieser Art der Forschung noch wichtige Ergebnisse erwarten!

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Discussion

F. Lenz (Göttingen): Herr v. *Verschuer* hatte sein Referat als «Methodischen Beitrag der Zwillingsforschung für die Humangenetik» angekündigt; er hat dann aber im wesentlichen nur über Ergebnisse der Zwillingsforschung, insbesondere seiner eigenen, berichtet.

Verschuer meint, ein großer Unterschied der Konkordanz einer Reihe eineiiger Zwillinge (EZ) gegenüber einer Reihe zweieiiger (ZZ) bewiese eine «spezifische Erbbedingtheit» des untersuchten Merkmals. Er hat diese seine Ansicht am Beispiel der Tuberkulose erläutert. Ich möchte ihn fragen, ob das Wort «spezifische Erbbedingtheit» bedeuten soll, daß die Resistenzschwäche gegen Tuberkulose durch ein einziges Gen (monogen) bedingt sei, oder daß wenigstens in allen Fällen diese Resistenzschwäche genetisch dieselbe (also nicht heterogen) sei. Andernfalls vermöchte ich keinen grundsätzlichen Unterschied zwischen «spezifischer» und »nicht spezifischer» Erbbedingtheit zu sehen.

Verschuer spricht öfter von Gleichheit der Umwelt bei Vergleichen von Zwillingsreihen. Nun kann zwar die Gleichheit des Erbes bei EZ-Paaren als sichergestellt gelten, niemals aber eine völlige Gleichheit der Umwelt. Daher kann man aus Unterschieden im Schicksal von EZ-Partnern, die anscheinend in gleicher Umwelt leben, nicht auf Einflüsse schließen, die außer Erbe und Umwelt für das Schicksal der Menschen wesentlich seien.

Ich bin mit *Verschuer* der Meinung, daß die meisten Fälle von Krebs nicht wesentlich erbbedingt sind. Wir wissen nun heute, daß ionisierende Strahlen und mancherlei chemische Stoffe sowohl Mutationen der Erbmasse als auch Krebs verursachen können. Da es sich um Trefferwirkungen physikalischer Elementarteilchen handelt, ist die Verursachung einer somatischen Mutation, die zu Krebs führt, im Einzelfall nicht zu beobachten. Grundsätzlich handelt es sich aber um Umweltwirkungen. (Ich habe übrigens schon 1921 die Hypothese aufgestellt, daß mutagene [«idiokinetische»], physikalische und chemische Einflüsse Mutationen somatischer Zellen und zerstörendes Wachstum, d. h. Krebs, verursachen können.)

Verschuer meint, bei der Entstehung von Unterschieden eineiiger Zwillinge spiele auch «autonome Variabilität» eine Rolle. Das Wort «autonom» bedeutet eigengesetzlich. Ich möchte ihn fragen, ob er damit eine andere Gesetzlichkeit als die des Erbes und die der Umwelt meint. Ich behaupte nicht, daß ein Mensch lediglich ein Produkt aus Erbe und Umwelt sei. Man kann aber durch Zwillingsforschung nicht beweisen, daß es außerdem nicht «autonome» Vorgänge gäbe. Auch das Gegenteil kann man durch Zwillingsforschung nicht beweisen. Die Zwillingsforschung gestattet keine quantitative Erfassung des Anteils von Erbe und Umwelt, wie ich in mehreren Arbeiten näher ausgeführt habe.

Verschuer sagt in seiner vorläufigen Zusammenfassung: «Die Diagnose ‚Erblichkeit‘ ist für ein Merkmal immer dann zu stellen, wenn die Konkordanz bei den zweieiigen Zwillingspaaren deutlich kleiner als bei den eineiigen ist.» Nun hat aber Dr. *Kallmann* bei mehreren EZ-Paaren «Mongolismus» stets konkordant gefunden, bei ZZ stets diskordant. Ich denke, auch *Verschuer* wird den «Mongolismus» deshalb nicht für spezifisch erbbedingt halten. Entsprechendes scheint noch von weiteren Entwicklungsstörungen zu gelten, deren Ursache man in einer Schwäche des Eiplasmas vermuten darf. Der Vergleich der Konkordanzen von EZ und ZZ bedarf daher stets der Kontrolle durch Berücksichtigung der sonstigen Umstände und Ergebnisse der Familienforschung.

O. Frhr. v. *Verschuer*: Erst nach Absendung des «Abstracts» meines Referates zum Druck erhielt ich Kenntnis von dem Inhalt von *Waardenburgs* Referat, das mich veranlaßte, auf eine nochmalige Darlegung der Schwierigkeiten und Fehlermöglichkeiten der

Zwillingsmethode zu verzichten, zumal diese Fragen in zahlreichen Arbeiten von mir bereits eingehend behandelt sind. Den methodischen Beitrag der Zwillingsforschung für die Humangenetik glaubte ich, am besten anhand von einigen ausgewählten Beispielen zur Darstellung zu bringen, wobei ich mich auf körperliche Eigenschaften beschränkt habe, da die Behandlung der psychiatrisch-psychologischen Zwillingsforschung für ein anderes Referat vorgesehen war.

Die mir wichtig erscheinende Unterscheidung zwischen einer «spezifischen» und einer «unspezifischen» Erbdisposition ist mir erstmalig bei der Bearbeitung der Befunde von *Diehl* und mir an tuberkulösen Zwillingen klar geworden. *Diehl* hat in seinen Tuberkuloseexperimenten an Kaninchenzuchten den Nachweis erbracht: Eine Erbanlage entscheidet darüber, ob die Lunge dieser Kaninchen gegenüber der tuberkulösen Infektion empfänglich oder resistent ist. Es ist deshalb wichtig, auch beim Menschen zwischen einer derartigen spezifischen erblichen Disposition (bzw. Resistenz) gegenüber Tuberkulose und den vielfältigen unspezifischen erblichen Modifikationsfaktoren (z. B. reizbare Konstitution, Habitus asthenicus, Organ- und Lokaldisposition, innersekretorische Veränderungen, Erbkrankheiten wie Diabetes und Schizophrenie) zu unterscheiden.

Zwillingspaare können nach den Umweltverhältnissen, unter welchen sie gelebt haben, gruppiert werden. Die eine Gruppe umfaßt dann Zwillingspaare, die unter sehr ähnlichen Umweltbedingungen stehen; die andere Gruppe umfaßt solche, die unter auffallend verschiedenen Umweltbedingungen stehen. Von einer völligen «Gleichheit» der Umwelt kann natürlich nie die Rede sein – ich selbst habe das immer wieder betont. Es kommt mir dabei gerade darauf an, auf die ungeheure Vielfaltigkeit des Umweltbegriffes hinzuweisen und vor voreiligen Kausalschlüssen zu warnen. Bei drei Gruppen von Krankheiten scheinen mir die pathogenetischen Beziehungszusammenhänge ganz besonders locker und schwankend zu sein: 1. Krankheiten, die durch eine Umsetzung von mikrophysikalischen Einzelerscheinungen in Vorgänge von makrophysikalischem Ausmaß entstehen. 2. bestimmte Fälle von Virusinfektionen, 3. psychosomatische Erkrankungen.

Der Begriff der autonomen Variabilität stammt von *Zarapkin*, einem Schüler von *Timofeeff-Ressovsky* (Zeitschrift für menschliche Vererbungs- und Konstitutionslehre, Bd. 23, 1939). Im übrigen verweise ich auf meine Darlegung «Die Zwillingsforschung als Methode der Genetik vom Menschen», S. A. S., Nr. 13–19, Bologna 1949.

Ich begrüße die Bemerkung von Herrn *Neel* und teile seine Meinung, daß die vollen Möglichkeiten der Zwillingsforschung noch nicht ausgeschöpft sind.

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DETERMINATION OF THE ZYGOSITY OF TWINS

By Norma F. WALKER

If the Twin Method is to be used in genetical research, the zygosity of the twins must be accurately determined and must always be determined objectively—never subjectively. Evidence for the establishment of zygosity for each pair of twins should be prepared as carefully as it would be for presentation in a court of law.

Some investigators feel that monozygotic twins can be recognized merely by looking at them or at their photographs, or by accepting the opinion of a friend or relative. It is true that some monozygotic twins are so alike that they can be recognized with little chance of error and some dizygotic pairs are so different that few mistakes are made, but between the two extremes there are many for whom errors in diagnosis can readily occur.

Monozygotic twins form a graded series, from those who are much alike, to those who are less alike, on to conjoined twins who are frequently so different that it was once thought that they were formed by the joining of two embryos. Many times in our work we have seen the possible errors of subjective diagnoses when one of us would by appearance classify a pair of twins as monozygotic varying slightly from each other, while a colleague would claim that they were dizygotic twins with a strong family resemblance. A subjective diagnosis is strongly influenced by the characters which happen to impress the examiner.

We have under way a study of twins, one purpose of which is the determination of zygosity. In this determination we are striving to avoid circular reasoning, such as has frequently been followed, particularly in the use of dermal configurations. As a primary basis for our study of the zygosity of twins, more than 1,300 twin placentas have been examined, injected with liquid latex and stored. The collection of placentas began in 1937.

Co-operating more recently in the project are Dr. *Irene Uchida* (Research Associate at The Hospital for Sick Children) and Prof. *D. B. W. Reid* (Associate Professor of Biometrics, University of Toronto). Four hundred pairs of twins are now being recalled for study, the oldest of whom are 19 years of age.

In our study the assumption is made that all dizygotic twins have either two separate placentas or a single dichorionic placenta, although we are constantly watching for any exception, should it appear. Monozygotic twins on the other hand may have (1) two separate placentas, (2) a single dichorionic placenta, (3) a monochorionic placenta with separate fetal circulations of the blood, (4) monochorionic with a common circulation, (5) monochorionic and monoamniotic with separate umbilical cords, (6) monochorionic and monoamniotic with a single bifid umbilical cord, (7) monochorionic and monoamniotic with a single umbilical cord. The assumption follows that all monochorionic placentas belong to monozygotic twins (although again we are constantly on the lookout for any exceptions).

Applying the *Weinberg* differential method¹ it was found that 28.2 per cent of our series are monozygotic twins and of these 25.7 per cent have dichorionic placentas.

We are testing the hypothesis that similarity and dissimilarity in general appearance between monozygotic twins is associated with their twinning time: the later the time of twinning, the less alike the monozygotic twins are. If this is true, we could expect to find that the most similar monozygotic twins have dichorionic placentas, while the dissimilar MZ twins would be the pairs with monochorionic placentas and a common circulation of the fetal blood, or with monochorionic and monoamniotic placentas. All additional analyses of each pair of twins are checked against the type of their placenta. The placentas therefore form an important reference basis for the tests used in establishing zygosity.

A battery of tests is being used for zygosity, but four of these criteria are of prime importance: (1) sex, (2) blood groups, (3) serum protein groups and (4) dermal patterns. The first three characters have simple patterns of inheritance and so afford a reliable basis. The dermal patterns are probably less useful, but have their own unique advantages. Each of the four criteria permits a certain proportion of twins to be definitely classified as dizygotic.

¹ All MZ twins = total of all twins — $\frac{\text{♀♂ twins}}{2pq}$, where p and q are the frequencies of male and female births in the total population. Frequencies of p and q: 0.516 and 0.484.

Sex

Based on the sex distribution about 50 per cent of the dizygotic twins can be shown to be dizygotic on the basis of unlike sex. (More exactly 49.95 per cent, where 2 pq have the value 2 [0.516] [0.484].) In other words there is about 50 per cent exclusion of monozygosity, for undoubtedly unlike sex twins are not monozygotic.

Blood Groups

In our study the blood groups being tested are the A-B, M-N, P, *Lewis*, *Kell*, *Duffy* and Rh which jointly with the sex factor give a minimum of 92.7 per cent exclusion of monozygosity. The minimum is here calculated on the basis that only the twins have been blood grouped, not the parents. In some instances we do have the blood groups of the parents and sibs. Also in the above calculation no account is taken of the subgroups A₁ and A₂, nor of the S-antigen, nor of the complete genotypes of the Rh factor, all of which increase the probability of exclusion of monozygosity.

The blood group determinations are carried out for us by Dr. *Bruce Chown*, of the Children's Hospital, Winnipeg, assisted by a grant from the National Research Council of Canada.

Serum Proteins

The indeterminancy of zygosity can be further reduced by establishing the serum protein groups of the twins. Dr. *Oliver Smithies* in 1955 described the existence of three groups of individuals on the basis of differences in their serum proteins shown by starch-gel electrophoresis. *Smithies* and *Walker* [1955] showed that the serum protein group of an individual is controlled by a pair of genes with incomplete dominance.

The serum protein groups are a new and useful factor in genetic studies, so I should like to digress for a moment to speak on them. The proteins characterizing the new groups are all haptoglobins—proteins with haemoglobin-binding powers—so that *Smithies* and *Walker* in a letter sent to *Nature* (1956) suggest that this system of serum protein groups be known as the Haptoglobin System. As outlined in the letter we suggest that the locus symbol be *Hp* and the genes *Hp*¹ and *Hp*². The notation for the system would then be as follows:

In selecting this notation numerals are used to prevent confusion between red cell groups and serum protein groups. The close similarity of the haptoglobins 2-1 and 2-2 (which differ considerably from haptoglobin 1-1) is reflected in the names.

Haptoglobin system of the serum protein groups

Old nomenclature	New nomenclature	Genotypes
Group I	Haptoglobin 1-1	Hp^1/Hp^1
Group IIA	Haptoglobin 2-1	Hp^2/Hp^1
Group IIB	Haptoglobin 2-2	Hp^2/Hp^2

Taking the frequencies of the two haptoglobin genes as being equal, the proportion of DZ twins excluded for monozygosity would be about 40 per cent. These frequencies will probably prove to be not far from correct. The total exclusion for sex, blood groups and serum proteins would then be almost 96 per cent (95.65).

Dermal Configurations

Although the use of dermal configurations has certain disadvantages, these patterns have points in their favor which demand their recognition as a method in the determination of zygosity. Dermal configurations are established at the third and fourth fetal months and never change, except in size of ridges, from that time on through to birth and to death. As with blood and serum protein groups there is no age factor.

The skin patterns can be easily studied and re-studied in much detail. Moreover dermal prints can be taken under circumstances when it may be impossible to secure blood samples or to have complete blood groupings done.

It has long been believed (*Galton* [1892]) that inheritance is a factor in the determination of the dermal patterns, although the mode of inheritance is not understood. One serious disadvantage in the use of dermal patterns is the fact that disturbance of growth at the third and fourth fetal months may bring about extreme modifications in the inherited patterns, as are seen in mongoloid imbeciles (*Walker* [1956]). So one must move warily in the use of dermal patterns, waiting for the results of careful analyses such as *Holt* [1952, 1955, 1956] is conducting. At the moment the glitter of dermatoglyphics may well be compared with the glitter of statistics, for in both instances they tend to be abused by workers not understanding their limitations.

Since by the use of placentas, blood and serum groups, the zygosity of a large number of twins will be objectively determined, it should be possible to assess the usefulness of dermatoglyphics in differentiating dizygotic and monozygotic twins, free of the criticism of circular reasoning.

In the past too frequently the classification of twins has first been based to some extent on their dermal patterns, it having been assumed that similar patterns indicated monozygotic twins, while dissimilar patterns showed them to be dizygotic. Having thus separated the two types on the basis of their dermal patterns, it was circular reasoning then to analyze the variations in the dermal patterns of the two groups of twins. Free of this criticism we hope to determine which of the various dermal characteristics, such as digital ridge counts, digital patterns, positions of axial triradii, etc., separate the two types of twins most completely, and what combinations of dermal patterns will discriminate best between them. In this way the value of dermatoglyphics in diagnosing zygosity should be brought out clearly.

Even for individual dermal characteristics it is necessary to consider the most satisfactory form in which to use the data. In what way should the basic items of information be expressed in arriving at some kind of suitable score? There are many difficulties in carrying this out since the dermal characteristics usually dealt with are made up of a number of types for each of which counts or measurements are made. For example in using the digital ridge count of whorl patterns, does the single or double count discriminate better? We believe that the single count gives the better separation. For the ridge counts of loops, should the ulnar and radial patterns be grouped together, thus ignoring the important differences between ulnars and radials, so clearly demonstrated when there has been disturbance in fetal growth, as in mongoloid imbeciles? These are some of the many questions which we are not yet ready to answer.

Intrapair Differences in Monozygotic Twins

Dr. *Waardenburg* in concluding his paper has asked: Do we agree with *Bronson Price* [1950] that intrapair differences are greater in monochorionic than in dichorionic MZ cases, due to the common circulation found in the monochorionic? The suggestion is that a common circulation may be imbalanced over substantial periods of time, with resulting differences in the twins' development during these periods. This point of view is based on the writings of *Schatz* who held that such imbalance was an initial cause of cardiac deformities.

Some answers to the question of intrapair differences in monochorionic and dichorionic MZ twins have been found by my colleague, Dr. *Irene Uchida*, in her study of heart anomalies in twins. Out of 21 pairs of twins studied for heart anomalies all were discordant. Of these 11 pairs were dizygotic, 10 pairs monozygotic. Of the monozygotic group we fortunately had in our series the placentas of four pairs and an accurate description of a

fifth. Two placentas were dichorionic (one composed of separate parts), three were monochorionic (two of which had been injected with liquid latex and a common circulation of the blood demonstrated). Of these five pairs of MZ twins, therefore, two at least had separate circulations and for them the initial cause of the cardiac deformities was definitely not a common circulation of fetal blood. (In the studies just mentioned the cardiological examinations were made by the Cardiac Service of the Hospital for Sick Children, on both members of each pair of twins, and included fluoroscope, electrocardiogram, X-ray, catheter and angiogram.)

I might add that over a 3-year period at The Hospital for Sick Children, Toronto, 1,125 new cases of congenital heart disease were admitted. Fourteen patients were members of twin pairs (1 in 80.4 patients). The frequency of twin pair births in Canada is 1 in 83.4 births. There is therefore no suggestion of an increase in congenital heart disease in twins.

As Sir *Ronald Fisher* pointed out this morning, it is only in the last ten years or so that the blood group systems have been available for genetic study. In the determination of the zygosity of twins they are unquestionably of great value.

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Discussion

F. Keiter (Hamburg): Wir sind von den aufgezeigten neuen Möglichkeiten der Zwillingsdiagnose wohl alle sehr beeindruckt. Es darf aber nicht aus den Augen verloren werden, daß logische Zirkeln nur mit polysymptomatischen Diagnosen auszuschließen sind. Wird anthropologische Zwillingsdiagnose *vollständig*, d. h. mit 100-150 Einzelmerkmalen betrieben, dann bleiben nach meiner Erfahrung keine Zweifelsfälle. Infolge des Prinzipes der Unabhängigkeit der Merkmale, betreffen auch pathologische Störungen der Ähnlichkeit bei MZ meist nur einen kleinen Teil des anthropologischen Befundes.

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GENETIC-STATISTICAL DATA ON THE PRESENCE OF SECONDARY OOCYTARY TWINS AMONG NON-IDENTICAL TWINS

By W. A. MIJSBERG

Several authors have expressed the opinion that non-identical twins do not consist of dizygotic (= fraternal) twins only, but that, moreover, a third kind of twins also exists. Such twins should arise from division of the ovum, each daughter cell being fertilized by a separate sperm (*Danforth* [1916]). According to *Fischer* [1919] this division should take place during fertilization.

Since it was assumed that the two daughter cells are provided with exactly similar genes, the twin partners arising from these cells should on the whole be more alike than is the case in fraternal twins.

When the division occurs after the spermatozoon penetrates the secondary oöcyte, the paternal influence on "fraternal" twinning can be explained (*Curtius* [1928]). Moreover, by accepting the 3rd kind of twins it is more easily understood why a multiplet may consist of some identical and some non-identical partners (*Curtius*). Evidently monozygotic twins and the 3rd kind of twins depend on the same tendency towards division and differ in the time of the latter's expression only.

If a 3rd type of twins really should exist then one may describe:

1. Primary Oöcytary Twins (P.O.T.). The two maternal cells arise from one primary oöcyte. Its 1st maturation division gives origin to a secondary oöcyte and a giant 1st polar body. In the 2nd meiotic division the latter cell divides into a fertilizable ovum and a small 2nd polar body. Paternal influence on the twinning is excluded. In the bat *Vesperugo noctula* O. van der Stricht [1904] repeatedly found 1st polar bodies of practically the same size as that of the secondary oöcytes. In some Platodes, *Francotte*

[1897] and *Wilson* [1925] described giant 1st polar bodies which after fertilization underwent normal development.

2. Secondary Oöcytary Twins (S.O.T.). From a secondary oöcyte an ovum and a fertilizable giant 2nd polar body arise. Since in man the 2nd meiotic division is completed after penetration of the sperm, paternal influence on this unusual division is possible. In some Echinoderms giant 2nd polar bodies were observed and experimentally induced (*Dalcq* [1924], *Lindahl* [1941]). Fertilization and normal development of both ovum and 2nd polar body was described by *Gustafson* [1946] in a sea-urchin. In the mouse, *Sobotta* [1895] sometimes found 2nd polar bodies of such large size that he suggested their fertilizability.

3. Uniovular Dispermatic Twins (U.D.T.). In this condition the ovum produced by normal meiotic divisions should be subject to a mitotic division. Paternal influence on this unusual division is possible. As far as I know there is no biological evidence of such an occurrence.

It goes without saying that in S.O.T. and in U.D.T. the penetration of a second spermatozoon is possible only when the formation of the perivitelline space is delayed.

From the foregoing it may be concluded that the occurrence of a 3rd kind of twins in man is possible. Proof of its occurrence might be derived from studying the frequencies of concordance of twin partners with regard to an allele which in the somatic cells of the mother is present in heterozygous condition.

The partners of U.D.T. are always concordant with regard to such a gene, since the two ova from which the partners originate result from a mitotic division of the ovum.

In S.O.T. matters are more complicated. It may easily be computed that in cases of pre-reduction of the gene in question, the partners are concordant. In cases of post-reduction, on the contrary, the partners are discordant with regard to the maternal gene.

In P.O.T. the twin partners are discordant with regard to the maternal gene studied, when the latter is subject to pre-reduction. In the event of post-reduction, however, there are equal chances of concordance and discordance of the partners.

The latter proportion of concordance and discordance is also present in partners of fraternal twins.

Evidently, in a sample of U.D.T., the frequency of concordance of twin partners with regard to an allele which in the mother is present sometimes in the homozygous, and sometimes in the heterozygous condition, is higher than in fraternal twins. In S.O.T. the same excess is expected

where pre-reduction of the gene studied occurred. The frequency of post-reduction depends on the locus of the gene in question; it may vary from 0 % to 100 %. In all types of non-identical twins the two fertilizable maternal cells are fertilized by separate spermatozoa. Hence a corresponding excess of concordance of twin partners of U.D.T., and eventually of S.O.T., is to be expected in random samples when studying a monomeric trait dependent on a pair of alleles which express themselves always, and always in the same way. As such, the different bloodgroup series are of great importance.

Supposing random mating, the expected frequencies of concordance with regard to the bloodgroups M-N in partners of fraternal twins and of uniovular dispermatric twins can be calculated. Using the frequencies of the underlying genes ascertained by *Schiff* and *von Verschuer* in the Berlin population the expected frequencies are 59.5 % and 75.1 % respectively. In a random sample of 244 pairs of non-identical twins in Berlin the authors mentioned [1931, 1933] found concordance in 62.3 % of the twins. This frequency exceeds that expected if all non-identical twins were fraternal twins. The probability that this excess should depend on chance only is .187. In the same sample the observed frequency of concordance with regard to the A-B-O series was also higher than is expected in fraternal twins. In this case the probability that the excess should depend on chance only is .274.

Erroneous admixture of monozygotic twins in the sample cannot be the cause of these excesses. For in 84 sets of twins of unlike sex, which are included in the sample, even higher excesses of concordance are found.

Dahr, Offe and *Weber* published [1941] data on the frequency of concordance with respect to bloodgroup P in 188 non-identical twins in Cologne. The observed frequency is not higher than could be expected if all twins were fraternal twins.

From the foregoing data it seems probable that non-identical twins consist of fraternal twins and of secondary oöcytary twins. For it is only in the latter type of twins that frequencies of concordance higher than, equal to or lower than in fraternal twins may be found.

More material ought to be collected. The parents should be included in the investigation in order to eliminate cases in which the mother is homozygous. In obstetrical clinics blood can easily be obtained from the umbilical cords of newborn twin partners. The blood of the mother can also easily be collected. The father, however, often proves obstinate!

By combined forces of all investigators interested in gemellologia, sufficient material might be collected to decide definitely if, in man, a 3rd kind of twins does exist.

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THE COLLECTION OF 300 TWIN INDEX CASES FOR A STUDY OF TUBERCULOSIS IN TWINS AND THEIR FAMILIES

By B. SIMONDS

Twin studies are often used to demonstrate the importance of genetic factors in human disease and it is therefore particularly important to examine the methods employed in these studies.

If the concordance rates in monozygotic twins for a particular disease are higher than those in dizygotic twins it is assumed that hereditary factors play some aetiological part in the disease. The validity of this assumption depends, amongst other things, on two main factors:

- (a) the correct diagnosis of the zygosity of the twins, and
- (b) the obtaining of an unselected sample of twins.

This paper is concerned with the problem of the selection of the twin sample.

There is no doubt that all twin studies endeavour to obtain an un-

selected sample of twins but the criteria by which the nature of these twin samples are judged are not always sufficiently stringent.

In examining twin samples two methods may be used to decide whether they are an unselected group.

(a) The twin sample can be analysed to see if the number of monozygotic twins is similar to that expected in any population of twins.

(b) The twin sample can be compared with the population from which it is drawn to see if the number of twins found is similar to the expected number. The expected number of living twins in the population is estimated by taking the number of twin births and correcting for their stillbirth rate and neo-natal death rate [1]. There should be approximately 2% of twins in a mixed population.

Though the first of these methods of checking twin samples is important, on its own it is not an adequate method of judging the representative nature of the twin sample.

Kallmann and *Reisner* in their study of twins and tuberculosis [2] calculated that there were 27.3% of monozygotic twins in the sample which they studied. Because this figure was closely comparable with the expected figure of 25.6% for the population of monozygotic twin pairs in an unselected American twin group they concluded that the tuberculous twins were a random sample. Thus the first of the aforementioned criteria was satisfied by their twin samples. If, however, their twin sample is examined from the point of view of the second criterion, i.e. comparing the twin index cases discovered with the population from which it was drawn, then the evidence for its random nature is less well established. *Kallmann* and *Reisner* collected their twin index cases from the resident population and new admissions of the tuberculosis hospitals and clinics in the State and City of New York. Using *McDougall's* figure of 0.5% for the incidence of tuberculosis discovered by mass radiography in the American population [3], a figure which is similar to that in Britain, it is reasonable to assume a tuberculosis notification rate in America which is also similar to that in Britain. One would therefore expect *Kallmann* and *Reisner* to have collected approximately 2,000 twin index cases with newly diagnosed tuberculosis during the five-year period of their survey. They state that 657 twins were reported to them. This apparent discrepancy needs more detailed analysis and explanation before it can be assumed that their twin sample is truly representative of the tuberculous twin population.

Since 1950 the author, under the auspices of the Prophit Committee of the Royal College of Physicians, has reinvestigated the problem of tuberculosis in twins.

At first it was thought that an unselected twin sample could be obtained by relying on chest physicians reporting all newly diagnosed patients who are twins. The co-operation of the chest physicians in London and the Home Counties was therefore obtained and reports of twins began to be received. A rough check of the number of tuberculous twins expected could be obtained from the tuberculosis notification rates and within the first year it became obvious that many were not being reported.

These twins were, however, investigated and 43 pairs collected in the above manner give the following results.

Table 1

	Monozygotic		Dizygotic	
Con.	7	50%	5	17.2%
Dis.	7		24	

This shows a 50 % concordance rate in monozygotic twins and a 17.2 % concordance rate in dizygotic twins. There are 33 % of monozygotic twins as compared with the expected 27 %.

However, as it was realized that the twins collected were only a small proportion of the total twins, the manner of collecting the twin sample was reviewed. The above method was modified so that the population from which the twins were drawn was known.

A. Fifty-one clinics co-operated in finding newly diagnosed tuberculous twins and the author was able to check the results personally. In these 51 clinics there were 7,633 newly diagnosed cases of tuberculosis, of which 116 were twins, i.e. 1.5 % or 1 in 65.2 persons. This is lower than the expected number of 2 % and therefore even this method of collecting the twin sample was not satisfactory.

Of these 116 twin index cases, 25 of their co-twins died in infancy, and there is insufficient information about a further nine. In nine, both twins were index cases. Thus it is possible to analyse 73 twin pairs. These give the following results.

Table 2

	Monozygotic		Dizygotic	
Con.	5	20%	14	29.2%
Dis.	20	80%	34	60.8%

This shows a very different concordance rate in the monozygotic (20 %) and dizygotic twins (29.2 %) than the first group of twins.

It was decided that the only way of obtaining all the twins in a given population was to make certain that all patients in the population were asked if they were a twin. Chest physicians in various parts of England co-operated; the full register of tuberculous patients was copied and all patients were written to directly asking them if they were a twin. The following results were obtained.

Table 3

	Replied Number	%	Twins Number	%
London	9,063	97.9	174	1.92
Provinces	12,188	96.8	231	1.90
Total	21,251	97.3	405	1.91

A total of 21,251 patients were written to and answers received from 97.3 %. Four hundred and five tuberculous twins were discovered which is 1.91 % or 1 in 52.5 persons. This is very close to the expected 2 %.

One hundred and seventy-two twins had a co-twin who died from non-tuberculous causes in infancy and there is insufficient information about 27 twins. In 11 twin pairs both twin partners are index cases. This leaves 195 twin pairs that it is possible to analyse, with the following results.

Table 4

	Monozygotic		Dizygotic	
Con.	15	27.8%	20	14.2%
Dis.	39		121	

In this twin sample there are 27.7 % of monozygotic twins, almost exactly the expected number.

None of the data are presented in this paper as a contribution to the problem of the role of inherited factors in tuberculosis. Without correcting for age, type of tuberculosis and without also taking into account contact with tuberculosis and whether the twins have lived together, they are probably misleading. They are merely given to illustrate the importance

of collecting a twin sample which is truly representative of all twins with tuberculosis.

As a reminder of the various concordance rates found the following table is given.

Table 5

	Total No. of Twin Pairs	% Monozygotic Concordant	% Dizygotic Concordant
(A) Twins drawn from an unknown population .	43	50	17.2
(B) Twins drawn from a population giving 1.5% of twins	73	20	29.2
(C) Twins drawn from a population giving 1.9% of twins	195	27.8	14.2

Thus those twins (group A) known to be from the most inadequate sample show the highest concordance rate in the monozygotic twins. In the twin sample (group B) which is also known to be incomplete but which nevertheless contains a higher number of the possible twins, the higher concordance rate is shown in the dizygotic twins. The twin sample which is thought to be a complete sample (group C) shows a higher concordance rate in the monozygotic twins than in the dizygotic twins.

Exactly why the above results are obtained is partly a matter of speculation. Firstly, in groups A and B many people are involved in collecting the twins and all of them may not use the same criteria for finding the twins. In group A it is probable that nearly all the concordant monozygotic twins have been reported but fewer of the discordant monozygotic and dizygotic twins have been reported. When the twins have been reported in a more careful way (group B) it is probable that more of both the monozygotic discordant twins and dizygotic concordant twins are reported; the majority of the twins which are not being reported are the dizygotic discordant twins. The main conclusion to be drawn is that in twin studies such as this it is essential to make sure that all the twins are found. This can only be done if the investigator is able to check the results and if the proportion of twins is found to be near the expected number. This has been done in many of the early German studies [4] and is also done by Slater in his recent study of psychotic illness in twins [5].

If the twins are to be analysed statistically in an attempt to assess the importance of hereditary factors in disease it is essential that a complete sample of the twins in the population is obtained.

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THE PERCENTAGES OF CONCORDANCE IN TWINS AND MODE OF INHERITANCE

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ERGEBNISSE AUS DER NACHUNTERSUCHUNG DER BERLINER ZWILLINGSSERIE NACH 20-25 JAHREN (VORLÄUFIGE ERGEBNISSE)¹

Von G. KOCH

Die Zwillingsnachuntersuchungen der Münsteraner Schule (von Verschuer) haben gezeigt, daß neue Ergebnisse aus der Zwillingsforschung erwartet werden können, wenn man nicht wie früher im Querschnitt auslesefreie Zwillingsserien untersucht, sondern im Längsschnitt die Lebensabläufe

¹ Durchgeführt mit Unterstützung der Deutschen Forschungsgemeinschaft.

der Zwillingspaare verfolgt. Erst die Untersuchung der Zwillingspaare in verschiedenen Lebensabschnitten und die Sammlung objektiver Unterlagen ermöglichen es, das oft vielfältige pathogenetische Krankheitsgeschehen in seiner Abhängigkeit von Erbe und Umwelt richtig zu erkennen und zu beurteilen. Für den psychiatrisch ausgerichteten und vorgebildeten Genetiker ergeben sich hier gewisse Parallelen zu der Längsschnittbetrachtung, die die Grundlage der mehrdimensionalen Diagnostik der *Kretschmer'schen* Schule bildet. Ihr Ziel ist es, alle Kausalfäden aufzudecken, die in jedem Einzelfalle an der Gestaltung von «Form und Funktion» beteiligt sind.

Ausgangsmaterial der eigenen Nachuntersuchung war das Zwillingssarchiv (1707 Zwillingspaare) des ehemaligen Kaiser-Wilhelm-Instituts für Anthropologie, menschliche Erblehre und Eugenik (Berlin-Dahlem). Nach Ausscheidung bereits untersuchter tuberkulöser Zwillinge (*Mitschrich*) und unvollständiger Akten verblieben 1312 Zwillingspaare, von denen 408 vor Kriegsende in Ost-Berlin und Ost-Deutschland wohnhaft waren, 904 Zwillingspaare hatten ihren Wohnort in West-Berlin und West-Deutschland. Durch Rückfragen bei den zuständigen Einwohnermeldeämtern konnte bei 570 Zwillingspaaren die Anschrift eines oder beider Paarlinge ermittelt werden. In 332 Fällen blieben sämtliche Nachforschungen ergebnislos. Von den 570 Zwillingspaaren konnte bisher als sicher festgestellt werden, daß 16mal beide Partner verstorben, 6mal beide gefallen sind. Von weiteren 69 Zwillingspaaren ist bekannt, daß in 38 Fällen ein Partner verstorben, in 31 Fällen ein Partner gefallen ist. Der Altersaufbau des Ausgangsmaterials ergibt sich aus Abb. 1. Die Ausfälle bei den weiblichen EZ- und ZZ-Paaren dürften in erster Linie dadurch zu erklären sein, daß die weiblichen Zwillingspaare inzwischen geheiratet haben und heute unter einem anderen Namen in den nach dem Kriege und nach der Teilung Berlins erneut aufgestellten Melderegistern geführt werden. Bei den männlichen EZ- und ZZ-Paaren dürften die Lücken auf Verluste im letzten Kriege und auf Abwanderung zurückzuführen sein. Für eine wissenschaftliche Auswertung stehen bis jetzt 221 Zwillingspaare zur Verfügung (Tabelle 1): 113 weibliche und männliche EZ, 108 weibliche und männliche ZZ. Das Durchschnittsalter des gesamten Zwillingsskollektivs beträgt 34,3 Jahre. In 115 Fällen wurden beide Paarlinge nachuntersucht, in 10 weiteren Fällen sind beide Paarlinge verstorben (8) oder gefallen (2). In 96 weiteren Fällen konnte nur 1 Paarling nachuntersucht werden, in 37 war dabei der andere Paarling verstorben (22) oder gefallen (15).

Aus der Abb. 1 ist ersichtlich, daß die Zwillinge in der inzwischen verstrichenen Zeit das heiratsfähige Alter erreicht haben und somit auch vor die Frage der Eheschließung gestellt waren. Psychologisch gesehen bedeu-

Tabelle 1. Übersicht über die Gesamtzahl der untersuchten (bzw. erfaßten) Zwillinge

	Anzahl der Paare	davon beide Paarlinge untersucht (erfaßt)	beide Paarlinge gest.	beide Paarlinge gef.	1 Paarling untersucht	der andere Paarling gest.	der andere Paarling gef.
EZ ♀	64	42	3	—	19	4	—
EZ ♂	49	20	2	2	25	6	6
ZZ ♀	60	32	1	—	27	8	—
ZZ ♂	48	21	2	—	25	4	9
Gesamtzahl	221	115	8	2	96	22	15

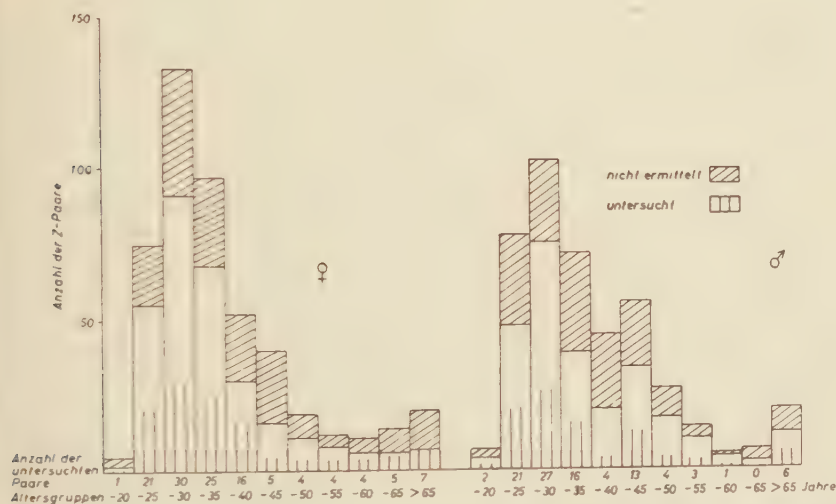


Abb. 1. Altersaufbau des Ausgangsmaterials (473 ♀ EZ und ZZ, 431 ♂ EZ und ZZ)
(West-Berlin und West-Deutschland)

tet die Eheschließung für die EZ die Aufgabe der Zwillingsgemeinschaft. Während sich die Eheschließung bei den weiblichen und männlichen ZZ – und auch bei den männlichen EZ – ohne Schwierigkeiten vollzog, ließ sich jedoch feststellen, daß die starke affektive Verbundenheit der weiblichen EZ in mehreren Fällen als ein die Eheschließung hemmender oder störender Faktor angesehen werden muß. In 3 Fällen war die Zwillingsverbundenheit stärker als das Band der ehelichen Gemeinschaft. Die Tatsache, daß in allen 4 Zwillingsgruppen in einem höheren Prozentsatz beide Paarlinge ledig geblieben sind, hat in mehreren Fällen seinen Grund in den schwierigen beruflichen und wirtschaftlichen Situationen Berlins. Bei den jüngeren Zwil-

lingen aller Zwillinggruppen, die zum Teil schon verlobt waren, kann noch mit einer großen Wahrscheinlichkeit mit einer Eheschließung gerechnet werden.

*Tabelle 2. Nerven- und Geisteskrankheiten (Gesamtübersicht)
(Nachuntersuchung Berliner Zwillinge)*

	EZ k	EZ d	ZZ k	ZZ d
Multiple Sklerose	—	1	—	—
Meningo-Encephalitis	—	1	—	—
Poliomyelitis	1	—	—	4
Debität	2	—	2	—
Krampfleiden	2	1	—	1
Schizophrenie	—	—	—	3 (1)
Psychopathie (Fehlreaktionen)	2	—	1	4
Summe	7	3	3	12 (1)

In Tabelle 2 sind die neurologisch-psychiatrischen Erkrankungen sowie die psychogenen Fehlreaktionen zusammengestellt, die in dem Zeitraum von 20 bis 25 Jahren, der zwischen der letzten Untersuchung und der jetzigen Nachuntersuchung verstrichen ist, bei den Zwillingen aufgetreten sind. Bei 4 Zwillingspaaren (2 EZ und 2 ZZ) konnte das Vorliegen eines leichten Schwachsinnzustandes festgestellt werden. Sie entstammten sozial tiefer stehenden Schichten und wiesen in den Familien weitere Fälle von Schwachsinn unter den Geschwistern und den Eltern auf. Bei den Krampfleiden zeigt die Längsschnittbetrachtung, wie die verschiedensten pathogenetischen Situationen und Konstellationen bei Vorhandensein einer ererbten Krampfbereitschaft zu Krampfanfällen führen können. Dabei ist die Krampfbereitschaft als die Summe aller pathophysiologischen Vorgänge innerhalb und außerhalb des Gehirns aufzufassen. Demgegenüber ist die Krampffähigkeit eine zwar hinsichtlich der Krampffreizschwelle unterschiedliche, aber doch allgemeine Eigenschaft des Gehirns. Es gibt Schädigungen des Gehirns, die bei jedem Menschen zum Auftreten von Krampfanfällen führen. In diese Gruppe gehört das diskordante weibliche EZ-Paar, bei dem bei dem Paarling I eine in der motorischen Präzentralregion vorhandene Hirnzyste als die Ursache des Krampfleidens festgestellt wurde. Als Beweis dafür, daß hier keine anlagebedingte Krampfbereitschaft vorgelegen hat, möchte ich erwähnen, daß es trotz jahrelangen Auftretens generalisierter Krampfanfälle hier nicht zur Entwicklung der für ein erbliches Krampfleiden charakteristischen konstitutionellen Merkmale im

Sinne der amorphen und pastösen Körperbauform gekommen ist. Beide Zwillinge wiesen bei der Nachuntersuchung im 38. Lebensjahr noch eine so weitgehende Ähnlichkeit auf, daß sie auch heute noch von der Umgebung verwechselt werden. Bei den konkordanten psychopathischen Zwillingen zeigte die Längsschnittbetrachtung, wie die Umweltverhältnisse und Katastrophensituationen der Kriegs- und Nachkriegszeit auf dem Boden einer erblichen Veranlagung die Fehlreaktionen und Entgleisungen und die kriminellen Handlungen geprägt haben. Es handelt sich bei diesen Zwillingspaaren um geistig einfache, umweltlabile Menschen, die mangels eigener geistiger Substanz den Prägekräften der Umwelt stärker ausgeliefert waren.

Die Gesamtübersicht über alle Geschwülste zeigt, daß in dem Zeitraum von 15 bis 25 Jahren, bei 14 EZ- und 13 ZZ-Paaren fast ausschließlich nur bei einem Paarling eine Geschwulst aufgetreten ist. In der eigenen auslesefreien Serie von Myomen sind sämtliche 9 Zwillingspaare (5 EZ- und 4 ZZ-Paare) diskordant. Es gibt innerhalb der großen und sicherlich nicht erblichen Gruppe der Myome lediglich einzelne, für deren Entstehung eine erbliche Disposition als mitwirkende Ursache angenommen werden kann, die in der eigenen Serie nicht in Erscheinung tritt (Tabelle 3).

Tabelle 3. Geschwülste (Gesamtübersicht)
(Nachuntersuchung Berliner Zwillinge)

	EZ k	EZ d	ZZ k	ZZ d
Karzinome	1	2	1	3
Uterusmyome	–	5	–	3 (1)
Ovarialzysten (-tumoren)	1	2 (2)	–	2
Andere benigne Tumoren	–	1	–	2 (1)
Hamartome	–	2	–	1
Summe	2	12 (2)	1	11 (2)
Verhältnis Konkordanz zu Diskordanz . .	2 : 12		1 : 11	

() in einer anderen Gruppe gezählt.

Ein «Zwillingsschicksal», bei dem beide Paarlinge zu gleicher Zeit an der gleichen Krankheit erkranken und etwa am gleichen Tage zur gleichen Stunde sterben, ist offenbar doch nur ein seltenes Ereignis. Der geringste Zeitunterschied, der zwischen dem Tode beider Paarlinge eines männlichen EZ-Paares, die beide das gleiche Grundleiden hatten, lag, betrug 1,7 Jahre. Im Durchschnitt (Tabelle 4) beträgt der Unterschied der Lebensdauer bei

Tabelle 4. Lebensdauer und Todesursache (vorläufige Übersicht)

Von 468 EZ und 436 ZZ sind	EZ	ZZ
Beide Paarlinge gestorben	11	3
Ein Paarling gestorben	18	18
Beide Paarlinge gestorben, durchschnittlicher Unterschied der Lebensdauer	7,9 Jahre	3,4 Jahre
Ein Paarling gestorben, durchschnittliche Überlebensdauer des anderen Paarlings . . .	12,1 Jahre	13,1 Jahre

den EZ 7,9 Jahre, bei den ZZ, bei denen allerdings die geringe Zahl berücksichtigt werden muß, 3,4 Jahre. Beim Tode eines Paarlings betrug die Überlebensdauer des anderen Paarlings bei den EZ im Durchschnitt 12,1, bei den ZZ 13,1 Jahre. Die Übersicht über die Todesursachen zeigt, daß es sich bei den EZ- und ZZ-Paaren, bei denen ein Paarling verstorben ist, in über 50 % um Infektionskrankheiten einschließlich der Tuberkulose und um entzündlich-septische Erkrankungen gehandelt hat. Wir müssen annehmen, daß für den Todeseintritt neben erblichen und Umweltfaktoren, zu denen auch im weiteren Sinne die therapeutischen Maßnahmen gerechnet werden können, auch psychische Einflüsse wie die eigene in der freien Willensentscheidung liegende Stellung des Kranken zu seiner Krankheit von Bedeutung sind. Die Annahme, daß bei den EZ der Tod des einen Paarlings auch den baldigen Tod des anderen als unabänderliches schicksalhaftes Geschehen nach sich zieht, findet durch diese Ergebnisse keine Bestätigung.

Tabelle 5. Todesursache des verstorbenen Paarlings (vorläufige Mitteilung)

	Infektions- krankheiten	Tbc.	Entzündliche- septische Erkrankungen	Geschwülste	Innere Leiden: Herz, Lunge, Kreislauf	Suicid	Un- glücks- fall	Unbekannt	Summe
EZ	4	4	2	1	4	1	—	2	18
ZZ	4	3	2	2	1	—	4	2	18
Summe	8	7	4	3	5	1	4	4	36

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UNDERSTANDING THE GENETIC CONSTITUTION OF MAN THROUGH THE STUDY OF CONSANGUINEOUS MARRIAGES

By H. M. SLATIS and R. H. REIS

Summary

Certain basic problems in human genetics can best be attacked through the study of consanguineous marriages. (1) A recessive genetic background can be inferred if an ailment has an increased incidence among children of related persons. (2) Knowledge about the mode of action of genes could be broadened; for example, if there are recessives that cause lethality in early embryonic stages, they might be demonstrable. Also, the frequency of genetically controlled stillbirth, low mentality, poor health, sterility, etc., could be observed. (3) Estimates could be made of the maximum number of ailments which could be found under given conditions of examination, and, thus, of the minimum number of observable gene loci. (4) Estimates of the average number of abnormal recessive genes carried heterozygously per person would be refined. (5) The risk of having abnormal children in consanguineous marriages would be accurately measured.

A number of consanguineous marriages have been ascertained at the time of marriage. Data on their subsequent family histories have been applied to analysis of the above problems.

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GENETICAL MORBIDITY OF CHILDREN FROM FIRST COUSIN MARRIAGES

By J. A. BÖÖK

Summary

Within a north Swedish geographical isolate all marriages between first cousins existing on 1st September 1947 were registered. The data comprise 34 such unions with 218 live-born children and 32 random control families with 165 children.

The fertility of the cousin parents agreed with the average of this population. The total mortality of the cousin and control children was about the same. The incidence of spontaneous abortions and stillbirths was lower in the cousin families.

Cousin parents tend to produce more intellectually defective and less gifted children than random control parents. The total genetical morbid risk for children from first cousin marriages was considerably increased, i.e. about 16 per cent against about 4 per cent for the control children. A method to estimate the prevalence of deleterious autosomal recessive genes in human populations is outlined. Tentative calculations indicate a minimum of three such genes in heterozygous condition per individual. The total number of different autosomal recessive genes (loci) with recognizable major detrimental effect in homozygotes in this population was estimated at between 150 and 450. These two latter estimates are only partly based on precise data, and should therefore only be accepted with great caution.

It should be emphasized that the results refer to a specific population. Pending further data from other populations they should not be generalized uncritically.

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VORLÄUFIGER BERICHT ÜBER DEN GESUNDHEITZUSTAND VON KINDERN AUS NAHEN BLUTSVERWANDTENEHEN¹

Von Edith RÜDIN

Die meisten Untersuchungen zu dem Problem der Blutsverwandtenehen gehen aus von den Kindern aus solchen Ehen, und zwar von kranken Kindern, von Patienten. Eine zweite Gruppe bemüht sich um möglichst vollständige Durchforschung sogenannter Inzuchtgebiete (z. B. *Hanhart* und *Böök*) und drittens wird der Prozentsatz consanguiner Ehen unter den Gesamtehen verschiedener Gebiete berechnet.

Wir dagegen sammelten eine Serie nahe blutsverwandter Ehepaare ohne auffällige Inzucht unter den Vorfahren möglichst auslesefrei, um deren Kinder zu beforschen.

Zu diesem Zweck suchten wir aus den katholischen Heiratsmatrikeln Münchens diejenigen zwischen 1870 und 1920 geschlossenen Ehen heraus, welche durch den Eintrag der kirchlichen Dispens als blutsverwandt gekennzeichnet waren. Wir gewannen so systematisch 417 Ehen im I./II. und II. kanonischen Grade der Blutsverwandtschaft. Davon konnten bis jetzt 181 Ehepaare, nämlich 175mal Vetter und Base ersten Grades und sechsmal Onkel und Nichte beforscht werden.

Nur zu 18 % (33 Paare) sind beide Eheleute gebürtige Münchner, beim größeren Teil war einer der Verlobten oder auch beide nach München zugewandert. Mehrfache Verwandtenehen unter den Vorfahren konnten nur bei einem Ehepaare festgestellt werden.

37 Ehen (20 %) blieben kinderlos. In 4 Ehen war die Ehefrau zu alt, dreimal wurde auf Nachkommen wegen der Blutsverwandtschaft der Eheleute verzichtet, dreimal aus anderen Gründen. In 6 Ehen wies ein Ehegatte

¹ Mit Unterstützung der Deutschen Forschungsgemeinschaft.

ein schweres körperliches Leiden auf, in 11 weiteren Ehen war die Kinderlosigkeit unbeabsichtigt und der Grund unbekannt. Zehnmal sind beide Ehegatten verstorben und über die Gründe der Kinderlosigkeit war nichts zu erfahren.

Aus unseren Probandenehen gingen 462 Kinder hervor, d. h. 2,5 Kinder pro Ehe. Dies ist eine verhältnismäßig niedrige Ziffer, weil ja ein großer Teil der Ehen vor 1900, also in einer noch kinderreichen Zeit, geschlossen wurde und weil die Eheleute vorwiegend den unteren sozialen Schichten mit bekanntlich höherer Fruchtbarkeit angehören. In einigen Fällen gaben die Probanden ausdrücklich an, nach Geburt eines gesunden Kindes auf weitere Nachkommen verzichtet zu haben, da ihnen das Risiko zu groß erschien.

Rund 53 % aller Probandenkinder blieben ledig, was mit dem Mittel der bayerischen Durchschnittszahlen von 49 % für 1946 und 60 % für 1910 ungefähr in Einklang steht. 47 % heirateten und hatten ihrerseits wieder 305 Kinder, d. h. 1,5 Kinder pro Ehe. 24 % der verheirateten Probandenkinder blieben bisher kinderlos.

Der Altersaufbau der bis jetzt beforschten Probandenkinder zeigt keine signifikanten Besonderheiten. Die Totgeburten betragen 5,4 % gegenüber dem bayerischen Durchschnitt von zirka 3,2 % in den Jahren 1888–1897 und 2,7 % für 1912.

Tabelle 1. Pathologische Befunde bei 462 Kindern aus Blutsverwandtenehen
Psychische Anomalien

Krankheit	Zahl der Fälle	Bezugs- ziffer	korrig. % Ziffer	korrig. % Ziffer in Gesamt- bevölkerung
Schizophrenie	2	269	0,7	0,8
Man. Depr. Psychose	3	222,5	1,3	0,4–1,0
Epilepsie	4	309	1,3	0,3–0,4
Schwerer Schwachsinn	2	423	0,5	1,0
Kretinismus	1	423	0,2	
Gewisse Zeichen des Mongolismus	1	423	0,2	
Minderbegabung	9	423	2,1	3,0
Suizid (bez. auf Tote über 15 Jahre)	2	80	2,5	1,4
Sonstige psychisch Abnorme	30	326	9,2	
Psychisch auffällig insgesamt	54		16,0	12,0–15,0

94 Probandenkinder (= Kinder aus nahen Blutsverwandtenehen) weisen irgendwelche Anomalien auf, das sind 20 %. Diese Anomalien sind im folgenden tabellarisch zusammengestellt.

Tabelle 2. Pathologische Befunde bei 462 Kindern aus Blutsverwandtenehen
Somatische Anomalien

Krankheit	Zahl der Fälle	Krankheit	Zahl der Fälle
Augenleiden angeb.	5	Tierfellnävus	1
Augenleiden erworben	3	Hirntumor	3
Schwerhörigkeit	1	Multiple Sklerose	1
Leukämie	2	Amyotroph. Lat. Skl. ?	
Blutungsneigung	2	(degen. Myopathie?)	1
Diabetes mell.	1	Ruhetremor d. linken Hand .	1
Diabetes insip.	1	Alterstremor	1
Drüsenstörung	1	Unklares organ. Nervenleiden	1
Spontane Muskelrisse	1	Spastische Beinlähmung	
Eunuchoidismus	1	von Geburt an	1
Sterilität	1	Lähmung als Kind, später	
Minderwuchs	3	verschwunden	1
Adipos. dystroph.	1	Körperbehindert (spinale	
Schwere angeb. Mißbildung .	5	Kinderlähmung?)	1

Eine besondere Begabung lag nur einmal vor, und zwar bei einem künstlerisch und literarisch sehr begabten Homosexuellen. Sie ist jedoch kaum das Ergebnis der elterlichen Blutsverwandtschaft, sondern entspricht dem hohen geistigen und künstlerischen Niveau der Familie.

Die Wiedergabe einer genauen Kasuistik ist hier leider aus Raumgründen nicht möglich. Dies ist um so bedauerlicher, als eine eindeutige Diagnosenstellung oft auf beträchtliche Schwierigkeiten stieß, da die betreffenden Individuen häufig schon geraume Zeit verstorben und genaue ärztliche Aufzeichnungen nicht verfügbar waren.

Zusammenfassend kann man also sagen: Wir finden unter den Kindern aus Ehen zwischen nahen Blutsverwandten vielleicht eine geringe Vermehrung psychisch abnormer Personen, sowie eine Anzahl anderer verhältnismäßig seltener Erkrankungen und Anomalien. Von den letzteren tritt meist jeweils nur 1 Fall auf, in ihrer Gesamtheit mögen sie im Vergleich zum Durchschnitt etwas vermehrt sein. Doch müssen wir auch in der Durchschnittsbevölkerung mit dem Auftreten einer Anzahl seltener Abnormitäten und Krankheiten rechnen, und so scheint uns die gesundheitliche Prognose für Kinder aus nahen Blutsverwandtenehen nicht derart besorgniserregend, wie mitunter angenommen, wenn sie auch im Einzelfall natürlich immer zweifelhaft bleibt.

Dies entspricht den Befunden anderer Autoren. So neigt *Hanhart* zu der Ansicht, daß in gesunden Familien selbst bei wiederholten Heiraten

zwischen Blutsverwandten kein Schaden für die Kinder zu erwarten sei. *Orel* fand 1934 in Wien bei den Kindern aus 520 nahe consanguinen Ehen keine wesentlichen Abweichungen vom Durchschnitt bezüglich Kinderzahl, Säuglingssterblichkeit und angeborener Mißbildungen. *Penrose* meint, wenn sich auch unter bestimmten Kranken ein beträchtlicher Prozentsatz aus consanguinen Ehen stammender Patienten finde, so sei doch umgekehrt auf Grund theoretischer und rechnerischer Überlegungen die Gefahr abnormer Kinder für das einzelne blutsverwandte Ehepaar nicht übermäßig groß, wenn auch zweifellos immer vorhanden.

Allerdings könnten unsere blutsverwandten Ehepaare eine gewisse gesundheitliche Auslese darstellen. Die im Volk verwurzelte Abneigung gegen eine nahe Blutsverwandtenheirat, die Angst vor kranken oder dummen Kindern, die ablehnende Haltung der katholischen Kirche erschweren bereits eine solche Eheschließung, und ein Leiden in der nächsten Familie mag dann vielleicht ausschlaggebend gewesen sein, die Eheschließung zu unterlassen oder doch auf Nachkommen zu verzichten. So scheint in den kinderlos gebliebenen Ehen eine etwas höhere Belastung mit Krankheiten zu bestehen.

Noch in anderer Hinsicht mögen die eine consanguine Ehe eingehenden Partner, und zwar vorwiegend die männlichen, eine Auslese darstellen. Wir fanden zahlreiche, offenbar gehemmte, schwer Anschluß findende Männer, deren Sexualität aber durchaus normal, häufig sogar sehr stark ausgeprägt ist. In 82 % aller Fälle stammten beide Verlobte oder einer derselben vom Lande. Sie fühlten sich in der Großstadt vereinsamt und suchten Anschluß beim Verwandten. Mitunter nahm ein verwitweter Mann seine Base oder Nichte zu sich, damit sie ihm den Haushalt besorge. In einem Drittel aller Ehen führte erst eine eingetretene Schwangerschaft oder die Geburt eines Kindes zur Heirat. Finanzielle Gesichtspunkte dagegen spielten selten eine Rolle, weil Vermögen meist nicht vorhanden war.

Noch ein Wort über die 305 Nachkommen der Probandenkinder, also über die Enkel der consanguinen Ehen. Auch sie scheinen in ihrer Gesamtheit nicht übermäßig auffällig, obgleich eine Anzahl von Anomalien vorkommt wie Hasenscharte, Situs inversus, Anencephalie, Schwachsinn und Taubstummheit. Zur Manifestation von Psychosen sind diese Nachkommen meist noch zu jung.

Zum Schluß sei nochmals betont, daß es sich hier um einen vorläufigen Bericht handelt, da die Untersuchung keineswegs abgeschlossen ist.

THE RANGE OF APPLICABILITY OF MULTIFACTORIAL GENETICS TO MAN

By F. KEITER, Hamburg (Germany)

As *Penrose* at the Bellagio Congress of Genetics very clearly exposed the classical Mendelian monomerics only are to be supposed where some well definable conditions are fulfilled. First, the trait must be distributed in a bimodal way (if not wholly discontinuous). However, anthropological traits very rarely show bimodality or discontinuity. Continuous unimodal, symmetrical distributions of the Gaussian type prevail to a great extent in anthropology. So the customary searching for Mendelian monomerics cannot longer be of much use to us. I, myself, brought these same arguments and some others in 1955 before I was acquainted with *Penrose's* text. The study of multifactor inheritance in anthropology is vitally needed.

We anthropologists must not longer consider multifactorial conditions as boring, troublesome or as inconsistent factors. We must try to find new positive ways out of that situation. Three main topics to be investigated are:

1. The different heritability (parent-child-correlations) in multifactorial traits.
2. The fulfilment of the mathematical consequences of normal correlation or deviations from it.
3. The combined behaviour of more than one multifactorial trait.

An important factor, hitherto unknown in anthropology is the problem of scaling, for only well scaled traits allow an exact multifactorial analysis. Auxiliary scales by way of estimation must be invented and proved where quantification by measurement and counting is impossible.

I. Different heritability (parent-child-correlation) in multifactorial traits.
The "Kritische Werte" (critical values, quotients of frequencies of the trait in parent-child-pairs and in pairs of people who are not related)* of 128

* *Keiter* in: Anthropologen-Kongreß Freiburg, Musterschmidt, Göttingen 1957.

anthropological traits have been found very different in a Hollerith-investigation covering 130 000 single data. Are there characteristic trends in the different behavior of the traits? Grouped according to technique we find on the average only little difference in measurements, undimensional estimations and dermatoglyphics. Only the heritability of pluridimensional traits (estimations of the degree of resemblance) is clearly higher.

Table 1. Critical values ("Heritability") of 128 anthropometric traits

Total		M	σ	m
		1.90	0.39	0.04
Grouped differently, to detect reasons for the different heritability				
Technics:	33 measurements	1.61	0.36	0.06
	53 undimensional estimations	1.65	0.42	0.06
	10 dermatoglyphics	1.73	0.35	0.08
	20 estimations of resemblance	2.11	0.33	0.08
	3 general impressions $M = 1.30, 2.40, 4.68$			
Reproducibility:	bad	1.66	0.40	0.06
	medium	1.74	0.33	0.05
	good	1.73	0.50	0.08
Change in growth:	no change	1.73	0.35	0.08
	little	1.72	0.48	0.10
	medium	1.74	0.39	0.06
	strong	1.55	0.41	0.06
Absolute size of the trait:	very small (about 1 cm.)	1.77	0.36	0.09
	small (about 3 cm.)	1.74	0.43	0.11
	medium (about 7 cm.)	1.69	0.45	0.09
	big (about 15 cm.)	1.65	0.35	0.09
	very big (about 100 cm.)	1.51	0.37	0.11

Grouped as *badly or well reproducible* we find the "best" traits not less variable in their heritability than the "worst", though on the average a little better. Thirdly, we try to group according to growth-behaviour in early and late maturing trait. The late traits (e.g. body size) show a worse heritability than the early (our material consisted of children from 2-10 years of age), but again the differences are restricted, the main source of the inequality of "Critical values" is still left undetected. The fourth grouping follows the *absolute smallness or bigness* in morphological traits. The bigger the trait the lesser is the heritability. In accordance therewith lessened variation-coefficients in bigger anthropological traits have been found in an

earlier investigation¹. But that interesting effect also is only of partial importance.

Further reasons for the differences found in the behaviour of multifactorial traits are: statistical insignificance, the non-genetical sources of variance, and, perhaps most of all the different adequacy of the auxiliary scales used. Differing genetical mechanisms must be supposed only after the exclusion of all the other fallacies hitherto mentioned.

Table 2. 44 anthropometric traits in 2-10-years-old children and their parents each scaled in σ and superposed on the same correlation table to show the exact fulfilment of the normal distribution (3815 cases)

	Midparents									
	+ 2 σ		+ 1 σ		0 σ		- 1 σ		- 2 σ	
+ 3 σ	-	-	9	3	7	1	1	-	-	21
	-	2	9	7	4	2	-	-	-	24
	1	4	5	10	16	9	6	-	-	31
	2	2	10	16	9	6	-	-	-	45
+ 2 σ	3	7	22	28	24	13	2	-	-	99
	3	4	13	24	30	12	4	1	-	91
	3	5	12	35	38	13	9	-	-	115
	3	3	23	47	44	28	12	2	-	162
+ 1 σ	3	10	43	78	76	45	19	4	2	280
	-	9	30	57	72	58	18	5	-	249
	1	8	22	61	75	53	20	8	-	248
	1	9	27	78	128	78	40	12	1	374
0 σ	1	12	28	108	184	140	56	15	1	545
	1	4	20	56	76	76	30	11	3	277
	2	5	21	43	68	77	37	11	1	265
	-	6	16	42	76	73	52	12	1	278
- 1 σ	-	8	12	40	82	85	66	12	3	308
	-	1	4	20	22	29	21	4	3	104
	-	-	3	16	27	28	20	7	1	102
	-	-	3	4	18	23	16	7	1	72
- 2 σ	-	-	1	7	14	30	13	7	2	74
	-	-	-	1	3	6	1	-	-	11
	-	-	-	1	2	3	6	2	1	15
	-	-	-	-	3	5	2	2	1	13
- 3 σ	-	-	-	-	2	2	4	4	1	13
	24	99	329	782	1093	886	450	126	22	

¹ In: "Naturwissenschaften" 1953, H. 7.

II. Fulfilment of the mathematical consequences of normal correlation. If the mathematical laws of normal correlation are identical with the basal law of multifactor inheritance, then such a basic law has not less certainty, is not less manifold, not less applicable than the classical *Mendelian* laws of inheritance. The consequences thereof have been previously discussed and cannot be repeated here ². It seems that they hold true very well in anthropology. Here only a correlation-table for the superposition of 44 metrical traits all scaled in their proper variance will be shown. It will be observed, that daring experiment gives an absolutely clear result. All the columns and rows show symmetrical normal distributions, the right upper and the left lower corners are left empty. The consequences of normal correlation are fulfilled.

To date I have never found a trait scaled exactly enough in human morphology which shows bimodality. Auxiliary scales for undimensionally estimated traits give always approximations to normal distribution as is shown by some examples. Exact scales must be free on both ends and must consist of equal steps, the gradation must be homogeneous. An example of the same trait in unidimensional but improper (not equally gradated) scale and in (more abstract) proper scale is shown. The toe patterns improperly scaled give quite an irregular distribution, while properly scaled they give an exactly regular and normal distribution.

Table 3. *Approximated normal distribution of undimensionally estimated physiognomic traits on auxiliary scales with five degrees (very low, low, medium, high, very high in per cent)*

Scale	- 2	- 1	0	+ 1	+ 2
Root of the nose (low - high)	2	25	33	36	5
Form of the nose (concave - convex)	2	30	49	16	4
Ear size (small - big)	2	17	70	11	0,5
Lobe of the ear (unfree - free)	2	23	27	35	9
Incisura intertrag. (narrow - wide)	3	25	45	24	3
Antitragus (flat prominent)	0,5	18	56	25	0,5
Corpus anthelicis (low - high)	4	24	41	28	3

Skewness of the distribution is sometimes affected by scales which are free at one end, but fixed or less free at the other end. Percentage scales with the mean of the trait near 100 or near 0 per cent often produce skewness. The variance increases and decreases if the room for possible varia-

² In: "Naturwissenschaftl. Rundschau" 1956, H. 2, and: Z. Morph. Anthr. 1954.

bility is broader or narrower itself. Symmetrical distribution requires practically unlimited range, or perhaps a range symmetrically limited at both ends. As has been said that condition usually prevails well enough in anthropological traits.

Anthropological traits of multifactorial character to date are found to fulfil the full consequences of normal correlation very well. They are always normally distributed in equigradated scales.

III. The combined behaviour of more than one multifactorial trait.

In general the simultaneous investigation of more than one trait in genetic science plays curiously little role. In some way the problem of paternity tests in anthropology has been the first task of a polysymptomatic character which has found broader genetical interest. Here we must define a maximal number of traits in the restricted area of the human body-surface. Two questions arise: what is the combination behaviour of traits lying in nearer or further *vicinity*, and what is the behaviour of traits in different *hierarchic level*? The first fully calculated correlation-matrix of a great number of multifactorial traits lying in near vicinity we owe to *Weidel* for 26 traits of the nose*. We see, that correlations already in so limited a vicinity are the exception and are found mostly in traits whose definition itself is only partially separated. As a rule the Mendelian law of independence of the characters holds true also for multifactorial traits as it holds true for the behaviour of single genes. A hypothesis on the reasons for this very important empirical fact will not be attempted. The theoretical implications are certainly of remarkable interest.

Different hierarchical level can arise from the manner of definition of the traits. Definition may always be further differentiated or more generalized. The entire size of the body may be investigated or the height of the head, of the throat, of the trunk, of the legs may be investigated separately whereby still further differentiations are possible. The resemblance of the nose in general in father and child may be estimated or the resemblance of 26 different traits of the nose may be separately estimated. Such are subjective hierarchies caused by definitions. But there are also objective hierarchies e.g. in a developmental sense. The muscle content in general is a hierarchically superior trait compared to the muscle content of the forearm.

* Formmerkmale der Nase und ihre korrelativen Beziehungen, Z. Morph. Anthr. 48, 1956.

Also: Dissertation Tübingen 1955.

The empiric facts show, that the behaviour of more generalized or more differentiated multifactor traits is not clearly different, the question of different hierarchical levels must not upset our action too much. That seems very bewildering at first. The more than simple solution is, that every single multifactorial trait *behaves according to its own variance*. Variance is the general scale for all sorts of multifactor traits, therefore in variance-scales they all show approximately the same behaviour. It may be, however, that the heritability is at a maximum on a certain level of differentiation or generalization. We have already shown above, that the more differentiated trait in morphology, the higher is its heritability. But certainly the differentiation can also be exaggerated. If heritability of a *single* finger pattern is calculated it is found to be less than the heritability of the sum of all the *five* patterns of a hand, still higher is the heritability of the sum of all *ten* finger-patterns. The sum for ten finger and ten toes however is no useful further generalization, the heritability is at its best at the ten-finger-level.

Multifactorial genetical theory not only covers nearly all non-pathologic, especially all morphologic human traits. It also provides us with many new starting-points for future work of great importance. It is not an end but a beginning. Consequences for the theory of hereditary diseases and anomalies are unavoidable, but will not be mentioned at present. Multifactorial genetics in anthropology show practical applicability in paternity diagnosis. Our polysymptomatic paternity tests rely theoretically on multifactor inheritance as serological paternity tests rely on classical *Mendelism*. The success of my own polysymptomatic test* in 80 % diagnoses on a 3 σ level is undoubtedly comparable with every test relying on classical Mendelism.

* Richtlinien für die Beurteilung von Vaterschaftsgutachten mit der Bilanzierungsrechnung, 1957. Selbstverlag Hamburg 20, Eisenlohrsweg 6. To be sent on request.

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COUNTING METHODS IN GENETICAL STATISTICS

By Cedric A. B. SMITH

Most parameters in genetical statistics are proportions. The frequency of a gene G is the proportion of genes at its locus which are of type G ; the recombination fraction is the proportion of gametes, derived from a double heterozygote, which carry a recombination. The ideal way of estimating a proportion is by direct counting. Unfortunately that is often impossible in practice, either because of uncertainty, as when recessivity makes GG indistinguishable from Gg , or because of loss of cases, as in the estimation of the segregation ratio of a rare recessive, when matings Gg , by Gg which produce no recessive gg offspring cannot be identified, and so are omitted from the count. A method of overcoming these difficulties is to take a provisional value for the parameter to be estimated, use it to count the expected numbers of genes, recombinants, or segregants, including the "lost" cases if any, and so obtain an improved value: this is now taken as the provisional value, and the process repeated until the provisional and improved values agree. This method is closely related to maximum likelihood, and can be readily adapted to give the standard error of the estimate, and to test its homogeneity in a series of samples.

These methods have already been described in part by *Cepellini, Siniscalco and Smith* in the "Annals of Human Genetics" 20, 97-115, 1955, and a further explanation has been published in 1957 (*ibid.* 21, 254).

GENERALIZED FORMULAE OF THE PENETRANCE CALCULUS

By C.-G. BERGLIN, Gothenburg (Sweden)

Trankell's penetrance calculus leads to general formulae applicable to monohybridic diallelia in the population. Under certain restrictions it is possible to solve all cases where one of the gene-factors is obligatory in the trait-carriers. It appears, however, that the solution often may require an investigation on three subsequent generations.

The penetrance calculus may also be applied to the calculation of gene-factors and genotypes in materials of paired siblings and twins, even for polyhybridic cases.

The mathematical discussion of both fields leads to a partition of the penetrance concept into two distinct sets, called genetrance and zygotrance. Genetrance refers to the ratio of the manifested quantity to the total quantity of a certain gene-factor in the population. Zygotrance refers to the ratio of the manifested quantity to the total quantity of a certain genotype in the population.

Formulae for probands to be published in "Acta genet. Med. et Gemell." 1957. For population formulae, see Acta genet. 5, 240-262, 1955.

Discussion

A. J. Bateman (Manchester): I should like, as a non-human geneticist, to say that I feel rather sceptical about the frequent use of the term "penetrance" in human genetics. In *Drosophila* or the mouse, we use the term in respect of a known major gene in which a proportion of the individuals *known* to be of the constitution *Aa* are phenotypically indistinguishable from *aa*. But even then the "penetrance" is not so much a property of the gene itself except in that some genes are very readily modified by the genetic background or environment while others are not. The penetrance of a gene under particular conditions is due to genetic segregation for modifiers and the variability of the environment and consequently in human genetics will vary from one family to another.

But there is a more serious criticism of the concept in the present studies. It is invoked whenever the hypothesis of simple dominance is inadequate, that is, whenever persons

not showing a character "pass it on" to their offspring. It may be that the major gene is being swamped by modifiers or it may be the character is fully polygenically determined. Unless there is good independent evidence that a single gene is involved the term penetrance should not be used.

A. Trankell (Gothenburg): The opinion has been expressed by Dr. *Bateman* that the concept of penetrance is used in Human Genetics to explain away certain discrepancies between genetical models and actual data. This may have been true earlier and is perhaps true in some cases to-day. The calculation of penetrance discussed by Dr. *Berglin* and Dr. *Huizinga* seems to show a way out of such difficulties. Its main principle is to construct mathematical models in which we take into account the variations of trait frequencies caused by factors outside the genes. Including these variations among the parameters we may be able to construct complete hierarchies of hypotheses or models which can be tested when actual data are treated. It has for instance been possible to show that the inheritance of handedness can be described by one single model in the system of hypotheses within monofactorial diallelia. Moreover this is valid for all known collections of data concerning the inheritance of handedness which can be used in population genetics. In spite of the fact that the materials in question were based on quite different criteria resulting in different amounts of recorded trait-carriers, the application of the model gives the same proportions of the alleles in the population. As far as I can see such calculations cannot be characterized as running away from inexplicable discrepancies but may be looked upon as very reasonable ways of handling observational data.

A. J. Bateman (Manchester): I wish merely to reply to the comments on my previous remarks. I had no wish to discourage such statistical studies. But the term "penetrance" should be used only for the percentage expression of a major gene. When there is no evidence of a single gene being involved I don't know what you should call it, I don't even know what it is.

Oakland, G. B.: *Acta genet.* 7, 67-70, 1957

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LINKAGE STUDIES WITH MULTIPLE ALLELOMORPHIC GENES

By G. B. OAKLAND

Since, in human genetics, the genes of a factor will be found in paired loci of homologous chromosomes, in linkage studies it will be sufficient to base the discussion on four alleles.

Represent the alleles by four points:

$$A_1 \bullet \qquad \bullet A_2$$

$$A_3 \bullet \qquad \bullet A_4$$

Any two points joined by an arrow show dominance. Absence of any connecting link between two points indicates lack of dominance. For purposes of enumeration transitivity is not assumed, i.e. A_1 dominant to A_2 , A_2 dominant to A_3 does not imply A_1 dominant to A_3 . If wanted this third relation must be explicitly specified.

Thus, in a system of four distinct alleles, between each pair of alleles there is no link or an arrow in either direction. Therefore there are

$$(1 + 2)^6 = 729$$

cases to consider, the successive terms of the expansion above giving the numbers of genetic systems with 0, 1, 2, 3, 4, 5, 6 dominance relations. Similar expressions apply to genetic systems with 3, 2 or 1 distinct alleles respectively.

Number of distinct genes	Dominance relations	total
4	$(1+2)^5 = 1+12+60+160+240+192+64$	$= 729$
3	$(2+2)^3 = 1+6+12+8$	$= 27$
2	$(1+2)^2 = 1+2$	$= 3$
1	$(1+2)^0 = 1$	$= 1$

Considerations of symmetry, permutations and designating parental genes will reduce the number in the first row to

$$1 + 1 + 4 + 10 + 9 + 9 + 4 = 38$$

But this is for only one factor! When two factors are considered in a mating such as:

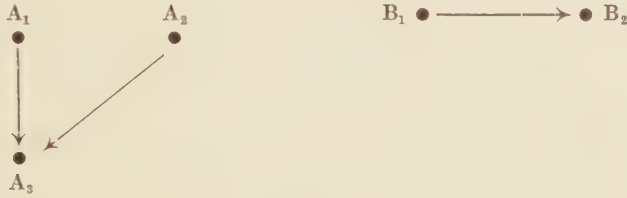
$$A_1A_2B_1B_2 \times A_3A_4B_3B_4$$

the number of possibilities becomes much greater.

Scores of the *Fisher-Finney-Bailey* type are developed here for mating types when both of the loci have a series of multiple allelomorphic genes and both factors show dominance. This paper considers in linkage detection

tests only families ascertained through the parents. Thus a sample of families is taken, the phenotypes of the parents determined and the families chosen for the record are those for which the genotypes of the parents are certain in the *Finney* sense.

If the A factor is the ABO blood group system and the B factor consists of two allelomorphic genes with B_1 dominant to B_2 , then the genetic system is:



There are 8 conceivable genotypes:

A_1B_1	A_2B_1	A_3B_1	$A_1A_2B_1$
A_1B_2	A_2B_2	A_3B_2	$A_1A_2B_2$

in the matings in this genetic system. The $8^2 = 84$ matings resolve themselves into 11 different mating types. If both parents are doubly heterozygous, it is convenient to list the scores, score corrections and amounts of information as though the recombination fractions were not equal. *Smith* did this in 1954 in "The separation of the sexes of parents in the detection of linkage in man". If then the assumption is made that $\chi_1 = \chi_2$, the two scores are added and the two amounts of information are added giving one score and its corresponding amount of information. *Finney's* recommendation that the small correlations between the two parts of the score be ignored is extended to the present case. For types 1 and 2, the same phenotypes are used in the same manner for the χ_1 and χ_2 scores and it is impossible to separate the contributions of χ_1 and χ_2 —hence only χ is shown.

In many matings in a genetic system, the probabilities of the phenotypes of the children are such functions of χ that each child can contribute something to the detection of linkage, provided the family size is greater than 1. In some matings however the probability of a particular phenotype makes it obvious that such children cannot contribute any information to the detection of linkage. For example a phenotype having a probability of $\frac{1}{4}$ would be in this category. In other matings the probabilities of some phenotypes are such functions of χ_1 and χ_2 that these phenotypes are

unable to contribute any information to the u-scores. A phenotype having a probability of

$$\frac{\chi_1 + \chi_2 - 2\chi_1\chi_2}{4}$$

makes no contribution to the u-score. For the detection of linkage the score is based on the conditional probability for families having children regardless of these phenotypes.

Hösli, P., A. Hässig and A. Franceschetti: *Acta genet.* 7, 70, 1957

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DETECTION OF LINKAGE BETWEEN THE GENES FOR THE BLOOD GROUP SYSTEM MNS_s AND THE GENE FOR PTOSIS CONGENITALIS HEREDITARIA SIMPLEX

By P. HÖSLI, A. HÄSSIG and A. FRANCESCHETTI

Summary

In Switzerland a pedigree of 103 affected people with hereditary congenital uncomplicated ptosis and irregularly dominant inheritance was described. More than 400 possible linkage relations were tested from data involving 34 serological and anthropological systems of chromosome markers and 130 sibpairs.

A highly probable linkage between the blood group system MNS_s and the gene responsible for ptosis is demonstrated.

The usefulness of the serological and anthropological chromosome markers is discussed.

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SUR UN CAS D'HÉRÉDITÉ D'APLASIE CIRCONSCRITE DU VERTEX AVEC INDICATIONS SUR LES GROUPES SANGUINS

Par R. HURON, J. RUFFIE, BAZEX et DUPRÉ

Introduction

Nous rapportons le cas d'une famille dans laquelle certains membres présentent une aplasie circonscrite du vertex dont nous avons pu suivre la transmission dans trois générations successives.

Cette famille d'origine italienne (Sandalo, province de Sombrio-Lombardie) est transplantée en partie dans la région toulousaine. Elle a été découverte à la consultation de la Clinique des Maladies Cutanées et Syphilitiques de l'Université de Toulouse (Prs. Nanta et Bazex).

On sait que ce type d'aplasie est rare; le nombre des cas cités ne paraît pas excéder une dizaine. A propos de cette famille une étude critique d'ensemble a été faite par *Peutat* dans une thèse dirigée par *Dupré* (Méd. Toulouse 1955); nous ne reviendrons pas là dessus dans cette note.

Etude sommaire de l'anomalie

Les plaques alopeciques ont un siège strictement sagittal (dans un seul cas existent deux petites plaques pariétales symétriques).

Nombre de plaques: il existe presque constamment 3 plaques (antérieure, moyenne et postérieure) bien alignées d'avant en arrière. Elles peuvent confluer ou être isolées. Dans deux cas existait une lésion unique et de petite taille.

La limite entre la lésion et la zone saine est nettement tranchée. Cette limite est d'ailleurs très irrégulière, présentant de nombreux diverticules. La surface de la lésion est faite de bosses et de sillons. Il peut exister une pigmentation plus ou moins marquée.

A la naissance, la lésion n'est généralement pas cicatrisée. Il existe donc une véritable plaie du cuir chevelu. La cicatrisation est dans la règle assez rapide: Elle se produit en trois semaines pour la plaque postérieure, en quelques mois pour la plaque moyenne et en un an et demi environ pour la plaque antérieure (qui, bien qu'étant la plus petite, cicatrise la dernière).

L'étude histopathologique faite chez un membre de la famille a démontré que ces lésions étaient conformes aux descriptions classiques et se caractérisent par:

1. l'absence de formation néovique,
2. l'absence de signes d'inflammation dermique,
3. l'existence d'un tissu de sclérose,
4. un certain degré d'atrophie épidermique,
5. l'absence totale de poils et de follicule pileux,
6. l'absence totale de glandes sébacées et sudoripares.

Matériel

La fig. 1 donne la généalogie d'une partie de cette famille. Nous avons indiqué sur ce diagramme les renseignements que nous avons pu recueillir sur les groupes sanguins des membres qui la composent. Les résultats de l'analyse sérologique sont donnée dans le tableau 1.

Discussion

Le fait que I_1 ait eu avec un homme normal 3 enfants anormaux et 4 normaux incline à penser que l'anomalie observée peut être schématiquement attribuée à un gène T dominant et que I_1 est hétérozygote. Le passage de la tare de II et III ne permet d'infirmer cette hypothèse. La figure 1 montre aussi que la tare n'est pas liée au sexe.

Le fait que I_1 ait des enfants OO (II_{7-9}) entraîne que le génotype de I_1 est AO et celui de I_2 : AO+BO+OO.

Le fait que I_1 ait des enfants ee ($II_{1-3, 5-9, 11}$) entraîne que I_1 est Ee. On voit aussi facilement que I_2 était MN et possédait les gènes O et e. Il est même très probable qu'il était ee. III_2 étant ceddee entraîne pour II_{1-2} les génotypes: CcDdee. Il est aussi évident que III_6 est CcDdee. On peut donc compléter la généalogie en y incorporant les éléments connus des groupes sanguins; les $C_i C_j$ indiquent les génotypes classiquement probables en posant comme nous l'avons fait ailleurs: $C_2 = CDe$, $C_5 = cDE$, $C_8 = cde$.

Liaisons absolues impossibles

T et M: III_4 n'est pas tarée et son gène M provient de II_3 qui l'est.

T et N: car autrement III_2 ne serait pas taré et III_6 le serait.

T et C: car autrement III_2 ne serait pas taré et III_6 le serait.

T et c: car autrement III_1 ne serait pas tarée.

T et D: car autrement III_6 serait tarée.

Si on admet les génotypes rhésus probables comme génotypes réels (ce qui dans notre cas nous paraît douteux) on voit tout de suite que T ne peut être absolument lié à C_2 ni à C_5 ni bien entendu à C_6 .

Rapports de T et A

Tous les tarés examinés sont A; II_{11} qui n'est pas taré porte aussi A, mais étant donné notre ignorance concernant I_2 il n'est pas possible de conclure à l'exclusion d'une liaison entre T et A.

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LA RELATIVITÉ DES NOTIONS MENDÉLIENNES CLASSIQUES DE DOMINANCE ET DE RÉCESSIVITÉ¹

Par J.-F. CUENDET et E. B. STREIFF

Il y a exactement 90 ans que le Père augustin *Gregor Mendel* publia son célèbre mémoire sur les lois de l'hérédité. Après avoir été longtemps méconnues, les «lois de Mendel» ont pris une importance capitale dans l'étude des caractères héréditaires. Aujourd'hui encore, elles occupent une place prépondérante. Cependant, il faut reconnaître que les notions classiques de dominance et de récessivité ne désignent plus des modes héréditaires opposés, mais seulement deux extrêmes d'une même chaîne ininterrompue de modes héréditaires variables.

D'après les lois classiques, l'hétérozygote Xx est toujours apparemment sain en cas de récessivité; il est toujours atteint en cas de dominance,

¹ Nous remercions vivement le Professeur *A. Franceschetti* et le Dr *D. Klein* dont les conseils nous ont été très précieux.

ne pouvant alors être distingué de l'homozygote pathologique. Or cette règle est infirmée par deux groupes d'exceptions fréquentes:

1. la pénétrance variable: l'hétérozygote est atteint dans un certain pourcentage des cas seulement;
2. l'hérédité intermédiaire: l'hétérozygote est pratiquement toujours atteint (comme dans la dominance), mais ne manifeste pas la même affection que l'homozygote (comme dans la récessivité).

1^o Pénétrance variable

Prenons l'exemple du nystagmus congénital. La très grande majorité des arbres généalogiques révèle une hérédité liée au sexe. Ceci se manifeste par l'absence de transmission pathologique de père à fils. Dans cette hérédité gono-chromosomique, on observe tous les termes de passage entre une récessivité complète et une dominance d'environ 73 %.

Fig. 1. Calcul de la pénétrance du gène nystagmique à partir des tableaux généalogiques de divers auteurs

Auteurs	Descendance des hommes nystagmiques			Descendance des femmes nystagmiques et hétérozygotes			Pénétrance moyenne (moyenne arithmétique des deux pénétrances précédentes)
	●	○	Pénétrance = $\frac{100 \bullet}{\bullet + \circ}$	●	○	Pénétrance = $\frac{200 \bullet}{\bullet + \circ}$	
<i>Hemmes</i> (arbre MM)	4	1	80 %	1	2	67 %	73 %
<i>Waardenburg</i> (Hemmes BB)	5	4	55 %	2	3	80 %	67 %
<i>Waardenburg</i> (Hemmes CC)	—	—	—	5	13	56 %	56 %
<i>Cuendet et della Porta</i>	4	3	57 %	4	12	50 %	53 %
<i>Clarke</i>	—	—	—	5	15	50 %	50 %
<i>Hanhart et Semadeni</i>	24	30	44 %	15	46	49 %	47 %
<i>Dubois</i> (Hemmes Z)	6	6	50 %	2	9	36 %	43 %
<i>Hemmes</i> (arbre HH)	1	2	33 %	5	20	40 %	36 %
<i>Cox</i>	3	3	50 %	1	8	22 %	36 %
<i>v. Kibort</i> (Hemmes R ₃)	3	5	37 %	1	14	13 %	25 %
<i>McGillivray</i> (Hemmes F)	1	10	9 %	1	16	12 %	10 %
<i>Engelhard</i> (Hemmes AA)	1	17	6 %	0	15	0 %	3 %
<i>Hemmes T</i>	0	5	0 %	0	14	0 %	0 %

Une série aussi continue de pourcentage de pénétrance pour une même affection, montre bien que dominance et récessivité ne s'opposent pas, mais sont simplement deux aspects extrêmes d'un même mode héréditaire.

Dans une même famille, la pénétrance ne varie généralement pas. Il existe cependant des exceptions intéressantes. L'un des arbres de Hemmes présente l'aspect d'une hérédité dominante dans une de ses branches et récessive liée au sexe dans l'autre. Certains auteurs, comme *R. R. Gates* ont échafaudé des théories compliquées pour expliquer cette exception apparente. Admettant une hérédité autosomale dans la branche à hérédité dominante, il est obligé de faire intervenir une translocation d'un gène autosomal au chromosome X chez l'ancêtre de la branche à hérédité récessive. *Franceschetti* a résolu le problème en admettant une même hérédité liée au sexe dans les deux branches, mais une pénétrance différente, soit 60 % dans une branche et 0 % dans l'autre. Ainsi dans une même famille et pour un même gène, l'hérédité peut être apparemment dominante pour une branche, récessive pour une autre. Ceci montre bien la relativité de ces notions. Car il n'y a pas 2 hérédités, il n'y en a qu'une, mais avec une pénétrance variable.

D'autres maladies comme la polydactylie, le diabète insipide, l'ictère hémolytique ont une pénétrance variable d'une famille à l'autre.

2^o Hérédité intermédiaire

Dans l'hérédité dominante, on admet classiquement que l'hétérozygote Xx a le même phénotype que l'homozygote XX. En fait, on ne connaît pas toujours l'homozygote. D'une part parce qu'il peut être très rare. Supposons une affection dont la fréquence dans la population (p) soit de 1/10 000. La fréquence des homozygotes, qui suppose un apport du gène pathologique tant du côté paternel que du côté maternel, sera de p^2 soit 1/100 000 000! Même si ce gène est plus fréquent, l'homozygote peut échapper à l'observation parce que le sujet qui en est porteur n'est pas viable. Les fausses couches ou les enfants morts-nés ne sont pas toujours examinés.

Or, les caractères transmis selon le mode intermédiaire sont plus nombreux qu'on ne le pense. Rappelons la dysmorphie des doigts. L'homozygote en serait ectromèle.

Rappelons l'anémie de Cooley ou anémie érythroblastique (T) ou thalassémie dont les modalités génétiques ont été récemment étudiées par *Franceschetti* et *Klein*. La forme mineure, souvent méconnue, correspondrait aux hétérozygotes; la forme majeure, généralement mortelle, aux homozygotes.

S'agit-il d'une dominance ou d'une récessivité? Quelle que soit l'hypothèse de calcul, le résultat est le même, ce qui prouve bien la relativité de

ces deux notions de dominance et de récessivité et le caractère typiquement intermédiaire de cette hérédité.

En effet, supposons qu'il s'agisse d'une dominance, puisque l'hétérozygote est toujours atteint, et essayons de prévoir quelle sera la descendance de 2 hétérozygotes.

$$\begin{array}{cc} \text{Tx} & \text{Tx} \\ \hline \text{TT} & \text{Tx Tx xx} \end{array}$$

T = gène pathologique de la Thalassémie

Nous aurons donc $\frac{3}{4}$ de sujets atteints, dont $\frac{1}{4}$ de la forme grave TT et $\frac{1}{2}$ de la forme bénigne Tx. $\frac{1}{4}$ des enfants seront indemnes.

Supposons au contraire que la forme grave de la maladie est récessive. Cette hypothèse se justifie par le fait que seuls les homozygotes sont atteints de la forme grave.

Le mariage de deux hétérozygotes donnera:

$$\begin{array}{cc} \text{Xt} & \text{Xt} \\ \hline \text{XX} & \text{Xt Xt tt} \end{array}$$

t = gène pathologique de la thalassémie

Nous aurons $\frac{1}{4}$ de sujets sains, $\frac{1}{2}$ de sujets hétérozygotes atteints de la forme bénigne, $\frac{1}{4}$ de sujets atteints.

Ainsi quelle que soit l'hypothèse de calcul (dominance ou récessité), les résultats sont exactement les mêmes et correspondent du reste à l'observation clinique.

Répercussions dans le pronostic génétique

La connaissance de ces exceptions aux règles classiques est importante dans l'établissement d'un pronostic génétique. Prenons à nouveau l'exemple du nystagmus congénital. Si une femme atteinte vient nous consulter, nous ne lui dirons pas que le 50 % de ses enfants seront atteints comme le voudrait une dominance rigoureuse; mais suivant l'arbre généalogique de sa famille, que le 25 % ou même moins risquent d'être atteints. Prenons en revanche une femme indemne. En admettant une dominance classique, nous lui aurions dit que sa descendance serait définitivement épargnée. En fait, nous devons lui dire qu'elle pourra avoir des enfants atteints dans telle ou telle proportion.

La connaissance de ces exceptions nous apprendra aussi à rechercher et à démasquer les hétérozygotes dans les familles à pénétrance incomplète comme dans l'hérédité intermédiaire.

Résumé

L'étude des pénétrances variables d'une part, de l'hérédité intermédiaire d'autre part, permettent de conclure que les notions de dominance et de récessivité ne sont pas contradictoires. Elles sont simplement les aspects extrêmes d'une même hérédité qui peut se déplacer de l'une à l'autre, restant le plus souvent dans une position intermédiaire. Cette position peut varier suivant les caractères transmis. Pour le même caractère, elle peut varier d'une famille à l'autre ou exceptionnellement à l'intérieur d'une famille. Les répercussions de ces considérations sur le pronostic génétique sont étudiées.

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L'IMPORTANCE DE LA GÉNÉTIQUE HUMAINE POUR LA MÉDECINE

Par L. GEDDA

(Plate I-IV)

Il y a déjà quatre vingts ans que *Mendel* a énoncé les lois héréditaires, et la génétique a été désormais, dans une certaine mesure, accueillie dans la médecine humaine, mais elle occupe encore une place provisoire, dans une dépendance plutôt que dans le bâtiment principal.

C'est la faute du temps, de la préparation, mais surtout de l'histoire de la science si la génétique est née dans un jardin de Brno, plutôt que dans un pavillon d'hôpital.

Mais c'est aussi notre faute à nous, les généticiens humains, qui aimons parfois circuler parmi nos collègues les médecins, masqués et drapés comme des ministres d'une science mystérieuse.

La génétique médicale n'est autre chose qu'une spécialisation de la médecine et elle a évidemment son droit, son langage, sa méthode et son expérience propres. D'ailleurs, il ne s'agit pas d'une spécialisation à arborisation terminale (c'est-à-dire fin à soi-même), mais plutôt d'un carrefour où toutes les branches de la médecine, l'une après l'autre, doivent passer et tirer des notions. Ce relatif isolement de la génétique au sein de la médecine est un facteur de retard que notre Congrès peut envisager et tâcher de résoudre.

Il faut jeter un pont, c'est-à-dire qu'il faut établir un langage qui puisse permettre une traduction des termes, des notions, des points de vue et des résultats de la génétique humaine, par rapport aux termes, aux notions, aux points de vue et aux résultats de la sémiologie, de la pathologie et de la clinique médicales.

Il faut donc procéder par des éclaircissements successifs qui sont, en même temps, des réciproques prises de conscience et des élargissements d'horizon de la médecine et de la génétique.



Fig. 2 [M]



Fig. 1 [L]



Fig. 7



Fig. 8

L'un des premiers points qu'il faut fixer c'est l'élargissement de la notion de maladie que la génétique engendre au sein de la médecine.

La notion de maladie dans la médecine courante est une notion individuelle qui est donc essentiellement circonscrite à l'individu. La maladie s'annonce avec de tels prodromes, commence avec de tels symptômes, elle établit et réalise son décours, ce cycle restant enfermé dans l'individu.

Il existe aussi une anamnèse familiale mais on n'y croit pas beaucoup; elle ne semble avoir que le rôle d'inspirer un diagnostic.

Par contre, dans la génétique médicale la maladie héréditaire est une réalité que chaque individu reçoit et transmet, une réalité qui dépasse l'individu, un caractère morbide de la souche que les différents individus peuvent révéler, à peu près comme un puit artésien montre l'existence d'une rivière souterraine. La maladie héréditaire est le résultat d'une mutation qui a frappé la souche à l'origine et qui circule dans les ramifications de cette souche; de ce point de vue, ce qu'on appelle des maladies ne sont en réalité que des syndromes. Elles sont des batailles dans le cycle de guerre déclenché par la mutation au sein de la souche, cycle qui constitue la véritable maladie.

Nous croyons qu'il serait le cas d'appeler ce premier principe avec une locution latine, à savoir: *continuum interhumanum morbi*; c'est-à-dire le principe de la continuité de la maladie parmi les consanguins.

La conception individuelle de la maladie est un mur invisible comme le mur du son, qu'il faut franchir pour arriver à recueillir les fruits que l'élargissement du concept de maladie peut produire. Le *continuum* réalise une dimension nouvelle de la maladie, qui permet d'abord de reconnaître sa véritable étiologie, et donc de voir si elle est héréditée ou acquise et, en ce dernier cas, si elle est ou n'est pas conditionnée par une prédisposition héréditaire ayant la valeur de cause concomitante nécessaire.

Par exemple, dans l'Institut Mendel de Rome, *Maltarello* et *Casa* ont observé un couple monozygote masculin dans lequel les jumeaux présentaient un mégacôlon hidyopathique concordant. Une plus large exploration dans l'espace familial a permis de constater qu'aussi la mère des jumeaux présentait un mégacôlon et très probablement aussi la grand-mère. Le cas est décrit dans mon volume commémoratif des lois mendéliennes et montre que la nature du mégacôlon hidyopathique est probablement héréditaire, du moins dans ce cas particulier.

Un cas singulier a été observé par *Gedda* et *Magistretti* chez un couple monozygotique féminin dans lequel seulement une jumelle présentait une paralysie du VIIe à gauche accompagné du phénomène des larmes de crocodile. On ne put découvrir aucune sorte de facteur étiologique au

dehors d'une très mauvaise condition concordante des dents; mais la récolte du répertoire familial vint aider à éclaircir ce cas. En effet, chez une sœur plus âgée, nous avons décelé, du même côté gauche, une paracinésie, consistant en un rétrécissement de l'ouverture des paupières et énophtalme dans l'abduction de l'œil gauche.

Revenant étudier le couple après cette découverte, nous avons mis en évidence la paracinésie gauche aussi chez les deux jumelles et chez la mère. Dans ce cas, la recherche du *continuum* a donc porté à deux résultats; le premier est nosologique, puisque nous avons confirmé que la paracinésie susdite peut être placée dans le cadre génétique de l'ophtalmologie; l'autre résultat est clinique, puisque il nous a permis de formuler l'hypothèse de l'existence d'un *locus minoris resistentiae* à gauche qui a favorisé l'implantation de la paralysie et du phénomène superposé des larmes de crocodile chez la jumelle qui était en des conditions de santé plus défavorables. Voici nos jumelles (fig. 1 [L] et fig. 2 [M]), dont l'une (M) présentait paralysie du nerf facial gauche; et voici la malade avec le phénomène des larmes de crocodile du côté gauche lorsqu'elle mange quelque chose froid et aigre (fig. 3).

L'étude de la maladie dans sa dimension familiale permet en outre d'établir le véritable cadre séméiologique, c'est-à-dire de dresser le catalogue des symptômes.

Ce catalogue pourra être dressé en rassemblant les formes *totales* (ou classiques) de la maladie, aussi bien que les formes abortives ou *microformes* et les formes qui peuvent caractériser les hétérozygotes, pour lesquelles nous utilisons le nom de *métaformes*.

Comme *Franceschetti* et *Klein* observaient lors du Symposium de Rome (1953), le dépistage des hétérozygotes, c'est-à-dire le dépistage des métaformes chez les porteurs hétérozygotes, s'impose de plus en plus. Par exemple, dans l'espace familial de deux frères porteurs d'albinisme oculaire, *Gedda* et *Magistretti* ont observé, comme jadis *Falls*, *Waardenburg* et *François*, chez la mère hétérozygote et chez d'autres femmes de la même souche des métaformes qui consistent dans une variation du fond de l'œil. Voici le proband (fig. 4) et son frère (fig. 5) qui présentent le fundus caractéristique de l'albinisme oculaire en sujet homozygote (fig. 6). Voici la mère (fig. 7) avec le fundus caractéristique d'un sujet hétérozygote (fig. 8). Les fils présentent aussi un nystagme qui manque chez la mère.

En poursuivant l'étude d'une maladie dans l'espace familial, nous arrivons souvent à modifier les limites mêmes de la maladie et ce processus peut acquérir la valeur d'une révision nosographique.

C'est le cas de certaines syndrômes qui ont été jusqu'ici décrites en

tant que cadres isolés et qui viennent aujourd'hui se grouper dans un plus grand cadre, avec une signification héréditaire univoque. Telle est la révision de la syndrôme de *Klippel-Feil* que j'ai entreprise récemment avec Iannaccone. En étudiant cette syndrôme sur le plan généalogique dans les 50 cas décrits dans la littérature et dans 5 cas personnels, nous avons pu découvrir un cadre héréditaire caractérisé par la fusion ou par la schise congénitale d'éléments axiaux, *philum* qui peut parfois produire la syndrôme des «hommes sans cou». Nous avons appelé cette maladie «Schisosinostosis axiale congénitale familiale».

Dans ce cadre, je peux maintenant vous signaler un couple jumeau dizygotique dont, à l'inspection, l'un des jumeaux présente torticolis congénital et l'autre pas. Les radiographies nous montrent, dans le jumeau avec la syndrôme du torticolis, des phénomènes de synostose des vertèbres cervicales et dorsales; chez le jumeau apparemment indemne une synostose cervicale, qui est présente aussi chez un autre frère plus âgé et rétenu normal, tandis que le père présente une cifose cervicale et une schise vertébrale. Nous pensons aujourd'hui qu'aussi des syndrômes du torticolis peuvent être comprises dans la schisosynostosis axiale congénitale familiale, laquelle peut évidemment présenter des variations relatives à la particulière souche atteinte.

L'étude du *continuum* permet enfin et surtout d'étudier le mécanisme de la transmission de la maladie, qui joue un rôle essentiel dans la notion même de maladie, de sorte que parfois il nous donne la possibilité de poser un diagnostic différentiel.

Par exemple, on établit la diagnose de surdité labyrinthique par la transmission dominante, tandis que la diagnose de surdité récessive est assurée par le *continuum morbi* du type récessif.

On peut souligner un deuxième principe pour mettre en évidence l'importance de la génétique humaine par rapport à la médecine. Ce principe concerne les caractéristiques qu'une maladie, ou bien une prédisposition héréditaire, peut présenter dans une famille donnée, en produisant une variation de la même maladie, ou prédisposition entre famille et famille. J'ai appelé ce deuxième principe avec la locution: *genius familiaris morbi*.

De même que l'étude du *continuum interhumanum morbi* enrichit la médecine du point de vue théorique et clinique, l'étude du *genius familiaris morbi* permet au médecin d'envisager et de résoudre maints problèmes.

Une sagesse anonyme et traditionnelle dit au médecin: «prends garde! il n'y a pas de maladies; il y a des malades». Or, la génétique médicale veut prouver et améliorer ce proverbe, en disant: «Il n'y a pas de malades; il y a des familles malades.» Rien ne peut éclaircir ce principe essentiel de la

médecine, mieux que le concept strictement génétique de la mutation, qui frappe une lignée en des temps, populations, circonstances et modalités différentes, en y produisant un résultat transmissible, mais qui peut être divers selon les cas et qui peut donc déterminer la variation nosologique. Je ne connais pas, du point de vue didactique, un argument aussi vrai et convaincant que celui-ci, bien qu'aujourd'hui les écoles médicales n'y fassent presque jamais recours.

La première conclusion à tirer du principe de l'étude des familles est que la variabilité du mécanisme de transmission peut varier d'une famille à l'autre pour une même maladie. A ce sujet, il faut dire qu'en appliquant à l'homme la théorie génétique élaborée dans le secteur naturaliste, et surtout en appliquant telle théorie aux maladies de l'homme, il faut s'attendre à une complexité bien plus grande, car l'homme a été beaucoup plus étudié que les végétaux et les animaux. Le schématisme des lois mendéliennes, et même la théorie du gène, ne doit pas être dogmatisé; une fois encore c'est le cas de s'en tenir aux faits et surtout au fait primordial du modèle de transmission que l'on peut repérer dans l'étude de l'arbre généalogique en question. Pour rapprocher le médecin à la génétique il faut lui apprendre à sonder le terrain familial et à y découvrir les constantes qui caractérisent une maladie dans un milieu consanguin. En outre du mécanisme de transmission le visage particulier de la maladie dans une famille se compose des notions que la génétique connaît sous les termes de pénétrance et d'expressivité.

Quant à la pénétrance, il s'agit d'une notion toute nouvelle révélée par la génétique, puisque la médecine a été jusqu'ici exclusivement phénotypique et donc une science qui ne pouvait tenir compte que des maladies déjà «pénétrées» dans le phénotype. Le concept de pénétrance est un cadeau que la génétique a fait à la pathologie humaine, en lui révélant l'existence d'un état morbide potentiel qui peut exister dans le génotype, bien qu'il ne soit pas pénétré dans le phénotype.

En pratique il n'existe pas de meilleurs procédés que de rapporter à la famille les données relatives à la pénétrance.

Nous avons une situation tout à fait différente pour le concept d'expressivité. Ici, sur le plan phénotypique, la médecine courante est bien plus riche et bien plus nuancée que la génétique médicale. L'observation de l'homme malade a été conduite jusqu'aux limites du possible, non seulement le long des lignes directrices verticales de la phénogénèse, mais aussi horizontalement, suivant les répercussions qu'un phénomène héréditaire morbide peut avoir sur d'autres appareils et équilibres, avec des mécanismes purement phénotypiques. De même, et dans tous les cas, l'expres-

sivité est un choix qualitatif et quantitatif de symptômes qui reflète le *genius familiaris morbi*. Les concepts cliniques de gravité et de prognose se rattachent en même temps au concept d'expressivité et à la physionomie que la maladie réalise dans le milieu familial.

Le *genius familiaris* peut en outre expliquer certaines données de la clinique qui dénoncent un choix de localisation.

Le plus grand service que la génétique peut rendre à la médecine réside dans les faits qui dénoncent l'importance des facteurs que nous groupons sous le terme de *genius familiaris morbi*. Il s'agit de constatations précieuses qu'on doit recueillir soigneusement pour en tirer une utilité clinique directe, pour la diagnose, la prognose et la thérapie.

Le *genius familiaris morbi* a aussi beaucoup d'importance pour les associations pathologiques héréditaires qui caractérisent une famille en dehors du *linkage*, en tant que simple phénomène d'addition génétique. L'étude de la morbidité humaine au point de vue héréditaire accroît de plus en plus les possibilités du diagnostic héréditaire et une étude à peine suffisante ne manque pas de déceler dans une seule famille plusieurs hérédités morbides, prémorbides et sousmorbides.

Dans un arbre généalogique que j'ai récemment décrit, nous observons que la fistula auris congenita, l'oxicéphalie et la thélébrachiphalangie sont mêlées. Deux jumelles monozygothiques par exemple, sont porteuses de fistula auris congenita et d'oxicéphalie. Il s'agit d'hérédité distinctes mais qui s'additionnent dans l'arbre généalogiques et cette addition caractérise le *genius familiaris* de cette famille. Le *genius familiaris morbi* se manifeste le plus ouvertement lors du croisement des consanguins. Sur le numéro spécial de *Acta Genetica et Statistica Medica* dédié au Professeur Kemp, j'ai décrit le cas d'une famille où les parents sont cousins et où, dans la même fratrie, il y a maladie de Little discordante chez deux couples jumelaires dizigotiques.

L'introduction à l'étude du *continuum morbi* et du *genius familiaris morbi* conduit à mettre en valeur le point de vue familial en médecine. Il s'agit d'un point de vue traditionnel dans l'histoire de la médecine, où l'intuition du médecin, sa mémoire et son œil clinique se mêlaient jadis empiriquement et pouvaient faire de la génétique médicale *ante litteram* dans l'âge pré-mendélien et pré-génétique. La socialisation de la médecine et la spécialisation très poussée viennent détruire le rôle professionnel du médecin de famille, et on ne saurait prévoir son retour. D'ailleurs, les considérations que la génétique médicale propose à la médecine sont tellement valables qu'il faut s'efforcer de rendre possible, et même d'améliorer, le relief médical des données qui analysent l'espace familial d'un

malade quelconque. Un détail que nous avons introduit dans la pratique clinico-génétique de l'Institut Mendel de Rome consiste dans l'abolition du terme «anamnèse familiale» que nous avons substitué avec l'expression «observation familiale». C'est encore peu, mais c'est tout de même indicatif. Dans le milieu professionnel d'aujourd'hui, le problème le plus sérieux est de faciliter la tâche du médecin mutualiste et au médecin spécialiste qui travaillent en routine, en mettant à leur disposition un rapport familial suffisant qu'il faut mettre au courant de temps en temps.

En vue de cela, notre Congrès pourrait poser et examiner la question. Par exemple, selon un modèle que nous avons à l'étude et qui est à votre disposition, on pourrait songer à faire un «carnet sanitaire personnel» («Carta sanitaria»), où les pages colorées seraient réservées au Rapport Familial des antécédants, des collatéraux et des descendants, tandis que les pages blanches initiales seraient évidemment dédiées à la pathologie individuelle du sujet, aux examens, au décours, à la thérapie etc. L'arbre généalogique servirait en même temps d'aide-mémoire et d'index: par conséquence un médecin qui recevrait un malade pourrait utiliser les données familiales recueillies par lui-même, ou par d'autres médecins, et les augmenter.

Je désire enfin signaler que la médecine peut tirer une utilité particulière de la génétique, au moyen d'une de ses méthodes traditionnelles de recherche, c'est-à-dire de la méthode des jumeaux. Cette méthode a un rôle principal, que tout le monde connaît, qui a une grande valeur pour distinguer ce qui est héréditaire de ce qui ne l'est pas, pour établir la variabilité de pénétrance et la variabilité d'expression quantitative et chronologique d'un caractère héréditaire quelconque etc. Un exemple classique vient d'être donné par notre Chairman, le Professeur *Stecher*, qui a décrit le premier cas de nœuds d'Heberden chez deux jumelles monozygotiques. Mais la méthode des jumeaux permet en outre d'améliorer la connaissance des maladies humaines dans leur cadre clinique ordinaire, c'est-à-dire dans leur résultat phénotypique.

Cette utilisation de la méthode des jumeaux au service de la connaissance de la pathologie individuelle est toujours fondée sur l'extraordinaire ressemblance des jumeaux monozygotiques, assurée par l'exakte correspondance de la formule génotypique. En ce cas particulier, la ressemblance peut servir à déceler des symptômes que l'absence d'un terme de comparaison ne permet pas d'habitude de découvrir.

L'école bâtit dans l'esprit du médecin l'image de l'homme moyen normal, auquel le médecin rapporte les formes et les fonctions de son malade. Mais il s'agit d'un modèle conventionnel assez pâle et sans relief,

tandis que le couple jumelaire permet de rassembler même les nuances et de leur donner une interprétation. En évaluant les contrastes dans le couple monozygotique, j'ai pu relever le symptôme radiographique de la stase cérébrale. C'est le cas des cojumelles monozygotiques de 13 ans dont l'une seulement présentait une cardiopathie en dé-compensation. C'est un cas analogue des sujets de 19 ans, où lors de notre observation un seul jumeau était hyposistolique.

Seulement une comparaison des radiographies des sujets monozygotiques, héréditairement identiques mais différenciés par la maladie, pouvait permettre de démontrer que la stase cérébrale, en dehors de ses symptômes classiques, se traduit aussi par une opacité plus accentuée aux rayons.

En effet, la pathologie des jumeaux monozygotiques, avec ses concordances extraordinaires et même, comme je viens d'exposer, avec les possibilités qu'offrent les discordances, exerce un extraordinaire pouvoir de conviction sur le médecin, pour le conduire à envisager et à encadrer les problèmes médicaux du point de vue génétique. C'est aussi pour cette considération qu'à Rome, nous tâchons constamment de favoriser les jumeaux, aussi du point de vue associatif et de l'assistance. Il s'agit d'un service pour les jumeaux, mais aussi d'une valorisation, vis-à-vis des collègues, de l'apport de l'étude des jumeaux à la médecine.

Allison, A. C.: Acta genet. 7, 87-90, 1957

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SUGGESTIONS FOR NOTATION IN HUMAN GENETICS

By A. C. ALLISON

Ford [1955], making a much needed attempt to present a uniform notation for the human blood group, makes the following comments:—

“The notation of the human blood groups is at present chaotic. Not only is it out of accord with that adopted elsewhere in genetics, but its usage is inconsistent from one blood group system to another. This adds unneces-

sary difficulties to the understanding of a subject which is decidedly intricate. Indeed, in the current literature it is often impossible to determine whether a given symbol refers to a gene or an antigen, and this confused terminology has certainly been a potent factor in preventing many geneticists from including the blood groups within their sphere of interest. Such a situation cannot continue indefinitely, and its revision is overdue..."

These remarks are true of human genetic notation in general. Hardly any two authors have used the same principles in developing a notation for the characters they have been describing. The confused state of human genetical notation becomes evident on examining such works as those of *Gates* [1946] and *Sorsby* [1953]. No distinction has generally been made between genes and their products, whether these be blood group antigens, haemoglobin types, abnormal amino acids in the urine, or other compounds. And characters have been frequently described as dominant even when there has been no opportunity to compare the heterozygote with the rare homozygote.

The total corpus of information on human genetics now assembled is enormous; many new characters—such as the serum haptoglobulin types—are coming to light; the theory of polymorphism, developed in other fields of genetics, is coming to have an important bearing on the subject; and cases of true linkage between genes controlling common marker characters and the genes of inherited diseases are being found. It is time that certain general recommendations with regard to terminology in human genetics were made. There seems to be a good case for having a standing international committee to advise on this subject. The committee could make and publish certain general recommendations, and the individual members would be available for consultation in their own countries. By example and sustained effort the committee should eventually succeed in developing a uniform and workable system of notation, as has happened in other fields of genetics (e.g. *Drosophila* and mouse genetics). Agreement on a system of nomenclature is all that is wanted; no decisions on priority should be taken.

I have certain general recommendations to offer. The type of notation advocated has already proved successful in the case of the abnormal haemoglobins:—

1. In genetical writings characters should be described as dominant only when the heterozygote has been shown to be indistinguishable from one homozygote. With most "dominant" human characters this is not the case, and it is sometimes known to be untrue. Thus, in brachydactyly and chondrodystrophy cases homozygous for the abnormal gene have been

found to be very much more severely affected than the heterozygotes. They should be termed "heterozygous effects". In lectures and discussions it may be convenient to employ the term "dominant" inheritance, but it should always be made clear that this is not true dominance.

2. Characters should be accepted as recessive or sex-linked recessive only when there is full genetical evidence that the inheritance is of this type. Thus, many heterozygotes are now distinguishable by minor abnormalities (e.g. renal diabetes insipidus and phenylketonuria discussed at this congress); and the fact that a character is much commoner in males than in females obviously is not enough to establish sex-linked inheritance.

3. Genotypes should be clearly distinguished from phenotypes. Genes should be italicized and gene products (where known) or phenotypes should not be italicized. The locus is indicated by one or two letters. Where a character is clearly established to be a recessive or a sex-linked recessive, the locus symbol can be in small letters (e. g. *h* for haemophilia), although there seems to be a case for abandoning this type of notation altogether. When a character is not recessive or sex-linked recessive, the one letter or the first of the two letters should be a capital. The allelomorph is indicated by the presence or absence of a suffix attached to the locus symbol, e.g. *Hb^s* for the sickle-cell gene. Letters, not numbers, should be used as suffixes. A capital in the suffix is dominant to a small letter in the suffix. When allelomorphs, each with a capital in the suffix, are brought together they both exercise their effects. Thus a capital in the suffix represents a gene which exercises its effect whenever present (the effect of one dose does necessarily equal that of two). A gene represented without a suffix is dominant in effect to one with a small letter in the suffix, but recessive to one with a capital in the suffix. A gene without a suffix is one whose product has not yet been recognized (and which may not exist).

4. Genetic linkage in man should be accepted only when the evidence for it is good. At least two methods of detecting linkage should be applied, and a high level of significance required, in view of the unavoidable element of selection involved in detection of linkage (many tests are performed and a few which *appear* significant chosen for further study). *Smith* [1953] has suggested that in the detection of linkage in man the significance level might well be placed at 0.001. Where several families are studied and show no significant heterogeneity, a less stringent level of significance might be accepted, since otherwise cases of loose linkage will be missed.

Many instances of sex linkage and of linkage among human blood group genes, and some cases of linkage of blood group genes with other

genes, are now known. At about this stage in the development of both *Drosophila* and mouse genetics, numbers were given to the linkage groups. This could be done also for Man, and it is suggested that they be given numbers in the order in which the common or polymorphic marker genes were characterized, viz:—

- I — sex linkage, total or partial
- II — linkage with ABO blood groups (1924)
- III — linkage with MN (1927)
- IV — linkage with P (1930)
- V — linkage with Secretor (1932)
- VI — linkage with taste sensitivity to PTC (1932)
- VII — linkage with Rhesus blood groups (1941)
- VIII — linkage with Duffy blood groups (1950)
- IX — linkage with Kidd blood groups (1951)

Other linkage groups should be numbered only when there is reasonably good evidence that new polymorphic characters are not linked with any of the above marker genes. Furthermore, marker genes should be present in all races. Thus, Lewis and Lutheran probably belong to linkage group V: and the genes for abnormal haemoglobins should not be used.

A discussion on Genetic Notation in Man was held on 4th August 1956. It was resolved that Dr. Allison's suggestions should be published in the Congress Proceedings so as to serve as an interim guide to investigators developing notations for new characters. It was resolved also that the suggestions should be considered by the Genetics Congress at Tokyo, 1956, and by the Greater Committee on Genetic Notation at the International Congress of Genetics at Montreal in 1958.

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THE INCIDENCE OF DIABETES AND ITS PREPONDERANCE AMONG WOMEN

By D. A. PYKE

This investigation started from the simple fact that more women than men have diabetes. Various explanations have been put forward to explain the difference, in particular that it may be related to the menopause, since it is after the menopause that the main sex difference appears, or that it may be because more women than men are fat.

However, it was first noticed over 20 years ago by *Mosenthal* and *Bolduan* [1933] that the excess of women was confined to married women. *Joslin, Dublin* and *Marks* [1936] confirmed this three years later, but attributed it to a greater tendency of married women to become fat. But it would seem to be more rational to examine the influence of parity, since pregnancy is the main physiological event separating most married women from single women.

In an attempt to discover whether parity is the factor responsible for the excess of women diabetics, I have examined the records of 953 patients attending the Radcliffe Infirmary, Oxford.

Their age and sex distribution, represented in fig. 1, are similar to those reported by many other workers. Up to the age of 45 or so the numbers are roughly equal, thereafter women outnumber men by about 2 to 1 until extreme old age.

We would, of course, expect to find some excess of women, as there are more women than men in the general population at this age.

By dividing men over the age of 45 into age groups, and correcting for the excess of women found in the general population a number can be derived for the women we would *expect* to find in each parity group. By comparing the number we *expect* with the number we *do* find in each parity group, we discover that the excess of women diabetics is confined to those

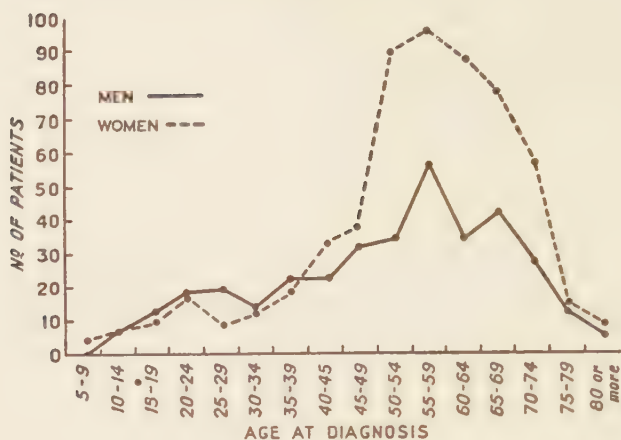


Fig. 1. Age-distribution by sex of 953 diabetics.

who have borne children and rises with increasing parity. This can be represented graphically (fig. 2).

The number of nulliparae is approximately that expected—111%—but the number of highly parous women is considerably greater than expected. There are more than two and a half times as many women with seven or more children as expected. These figures are rather lower than those given in an earlier paper, but are, I think, less inaccurate (*Pyke [1956]*).

The menopause cannot explain the preponderance of women diabetics. If it were the cause, an excess of women would be expected in all parity groups.

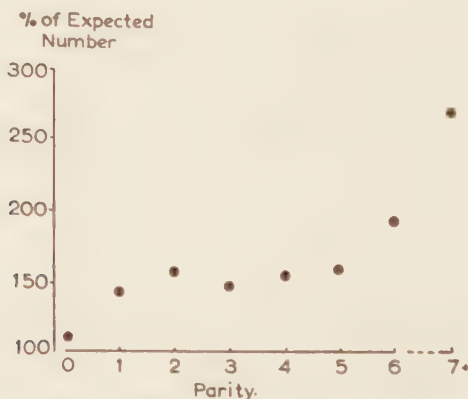


Fig. 2. Increase of incidence of diabetes with parity (women over the age of 45).

It might be argued that the effect of parity is due to an association with obesity. Women with children tend to be slightly heavier than women without, perhaps that could be the reason for the effect of parity.

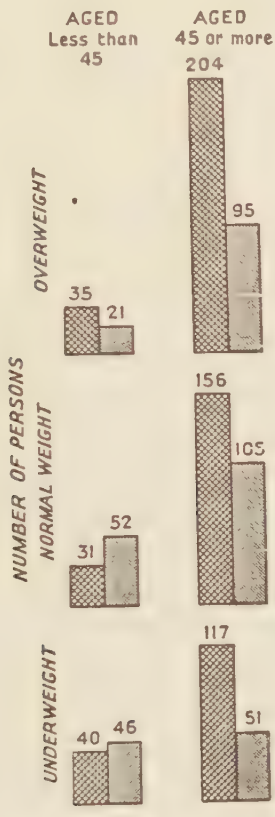


Fig. 3. Sex-incidence of diabetes in relation to age and build. In patients aged 45 or more there is a preponderance of women (hatched) over men (stippled) among the normal and underweight as well as among the overweight.

That this is not so is shown by the fact that women outnumber men among those who are of normal weight and underweight as well as among those who are overweight. In fig. 3 patients are divided into those under and over 45, overweight, normal weight and underweight. Women are shown in the hatched columns and men in the plain columns. In all weight categories women outnumber men.

Parity does not lead to the earlier appearance, or rather diagnosis, of diabetes.

Table 1. Age at diagnosis of women over 45 in relation to parity.

Parity	No. of women	Average age at diagnosis (yr.)
0	91	60.4
1	69	59.0
2	89	60.4
3	58	60.6
4	44	60.7
5	27	59.0
6	25	63.7
7 or more	60	63.3

The next point to be considered is whether parity uncovers a potentiality for diabetes or actually causes the disease. If it uncovers a potentiality we would expect to find that as many women would have a positive family history as men. If, on the other hand, parity *causes* diabetes we would expect to find that fewer women than men would have a family history of the disease.

Table 2. Patients with positive family history of diabetes.

	Percent
Men	28.6
Women	32.5

The percentage of women in our whole series with a positive family history is actually a little higher than the percentage of men.

This suggests that the effect of pregnancy is to uncover a potentiality for diabetes, not to cause the disease. But it is interesting to examine the incidence of a positive family history among women in relation to parity.

Table 3.

		Number with Family History (Percent)	
Parity			
Women	0	35	(114)
	1 and 2	32.4	(195)
	3+	28.5	(244)
Men		28	(291)

(Patients aged 45 or more at diagnosis).

35% of diabetic women over the age of 45 who have had no children have a family history of diabetes. But among those who have three or more children only 28.5%, have a positive family history, although this figure is still higher than that for men, among whom 28% have a positive family history. These differences are slight, but they are similar to those found by *Munro, Eaton and Glen* [1949] and may be real.

The association between parity and the incidence of diabetes has some bearing on our estimate of the frequency of potential diabetes in the population.

Spiegelman and Marks [1946], working with American figures, estimated that 2% of men develop diabetes before they die. We have seen that the incidence of potential diabetes among highly parous women is about two and a half times that in women without children, or in men. If the disease is genetically the same in multiparous women, nulliparous women and men, the incidence of potential diabetes in the population must be about 5% or more.

The finding of the aetiological importance of parity does not explain the observation of *Harris and McArthur* [1952] that the incidence of diabetes in women has increased in the present century. In 1900 the sexes were equal but now women outnumber men by at least 3 to 2. It can hardly be said that pregnancy is an invention of the 20th century!

I conclude that the excess of women among diabetics is due to the effects of parity and not to menopause or obesity; that the incidence rises with increasing parity, and that since the diabetes which pregnancy uncovers in multiparous women is probably the same genetically as that in nulliparous women and in men the incidence of potential diabetes in the general population is of the order of 5% or more.

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Discussion

C. O. Carter (London): Would Dr. *Pyke* please tell us what were the types of diabetes in his series of mothers, mainly severe or mainly mild or how many of each.

A. G. Steinberg (Cleveland, Ohio): I should like to ask Dr. *Pyke* to define family history as he used it and also to mention that there are data indicating that there may not be an excess of female diabetics in older age groups. These data derive from two types of studies (a) those in which the data are collected at an institution whose patients come for reasons other than diabetes, and (b) surveys of complete populations in which all members of the population are *examined*.

I may mention also that I have examined the frequency of diabetes among relatives of diabetic patients separated into 4 categories of severity. There was no indication of an association between the frequency of diabetes among the relatives of the diabetic patient and the severity of his diabetes.

D. A. Pyke (Oxford):

To Dr. *Carter*. The patients were of all types of diabetics, no clinical distinction had been made.

To Dr. *Steinberg*. By a positive family history is meant merely that the patient knew of an affected relative. A detailed analysis, moreover, showed that the number of parents, sibs and other relatives affected were very similar for men and women. The material was drawn from the Radcliffe Infirmary, Oxford, which was the only general hospital in the area and where between 80 and 90% of the known cases of diabetes were referred.

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HEREDITY IN DIABETES MELLITUS

By J. GRUNNET

I have the honour to tell you about an investigation, undertaken during recent years at the Copenhagen University Institute for Human Genetics, whose chief is the president of the Danish Organizing Committee of this Congress, professor *Tage Kemp*, under whose guidance I have studied the heredity of diabetes mellitus.

To tell you all about this investigation would be impossible in such a short time, but I hope within a year to send out a book to all university libraries, where those who are specially interested in the matter can read all about it, but here I shall be glad to give you a summary of my results.

First a few words about the incidence:

In order to ascertain the incidence of a disease one has to register the frequency of new cases in the population for a prolonged period.

This has not yet been done in Denmark.

In Norway Dr. Per *Hanssen* has done so for a period of 16 years in the town of Bergen with some 100,000 inhabitants.

For Copenhagen we have calculated the incidence—and in five-year-groups (0-4, 5-9, 10-14 years and so on) computed the quotient of diabetic persons.

By adding these percentage we have what is termed the cumulated incidence, and that is just the same as the morbid risk.

In fig. 1 and 2 the observed morbid risk for the population of Bergen (N_B) and the calculated morbid risk for Copenhagen (N_D) are indicated. A calculated morbid risk will often be too small, as not all cases are discovered. This figure tells us that if all people lived till they were 80 years old, some 6 or 7 per cent would become diabetics.

Here I may add that I can confirm the observations of Dr. *Pyke* that after the age of 45 years there is an excess of diabetic women.



Fig. 1. Morbid risk of relatives of probands with severe diabetes.

In my investigation I have divided the diabetic probands into two groups: those with severe and those with mild diabetes, because I suggested they were different which they proved to be.

In the same way as mentioned before we have computed the morbid risk of the relatives of diabetic probands.

In figure 1 the morbid risk of relatives of probands with *severe* diabetes will be seen. I may mention that the curves for grandparents and for sibs of parents are similar to those of the parents and are omitted in order not to have too many lines in the figure.

It will be observed:

Children of a person with a severe diabetes have a $9\frac{1}{2}$ per cent chance of developing diabetes, *prior* to the age of 35 years. Siblings of a person with severe diabetes have a 12 per cent chance of developing diabetes *prior* to the age of 65 years, and parents of a person with severe diabetes have an 18 per cent chance of developing diabetes if they live long enough.

In fig. 2 the corresponding figures for the relatives of probands with *mild* diabetes are shown.

It will be observed that the morbid risk for parents and siblings follow the same course.

Here the sibs reach 22 per cent before 80 years of age.



Fig. 2. Morbid risk of relatives of probands with *mild* diabetes.

Though these figures are very interesting time will not permit of further discussion, and I will now give you the conclusion of my investigation:

(1) The much higher incidence of diabetes among the relatives of diabetic probands than in the normal population indicates the pathogenetic role of heredity.

That confirms what we already know—especially from studies of diabetic twins. In this connection I want to say that such a study of diabetic twins will not be possible in Denmark. In the University Institute for Human Genetics we register all twins and all hereditary diseases—, and we have only 30 diabetic twins.

(2) The fact that the curve of morbid risk for relatives of probands with severe diabetes are different from those with mild diabetes tells us that the two types of the disease are different from a genetical point of view.

This is a capital point.

And that means to me that we can no longer talk about diabetes and diabetic problems without stating whether we are talking about severe or mild diabetes or a mixture of these.

There is a genetical difference between the two types: the mild and the severe diabetes.

(3) *Fig. 1* shows that the incidence of diabetes among the siblings of probands with severe diabetes is so much higher than that of the parents.

That may indicate that the severe diabetes is a simple Mendelian recessive disease.

Fig. 2. For the mild diabetes the increase of diabetic incidence for parents and siblings is equal.

That might mean that the mild diabetes is a simple Mendelian dominant disease.

This might lead to the conclusion that the mutated gene homozygotic will give severe and heterozygotic gene mild diabetes.

It may be so,—but I think this is too simple a solution of such a complicated matter.

We have to remember that diabetes is no uniform disease, and etiology and pathogenesis are not the same for all cases.

A minority are entirely exogenous and not hereditary at all. Others—especially the mild diabetes in older people—are probably due to heredity but provoked by exogenous factors. We have heard Dr. *Pyke* tell us about the role of pregnancy. That, I can confirm. Obesity, infection, stone in the gall-bladder or in the pancreas itself are often also provoking factors. Even those cases which are entirely endogenous may be of different origin: An endocrine disorder elsewhere may produce diabetes that cannot be distinguished from a primary pancreatogenous diabetes.

I think we cannot make one single mutated gene responsible for all that.

From all we know to-day about diabetes, we must consider that the majority of the cases are inherited—depending on several mutated genes—probably recessively inherited—and: the constellation and the number of mutated genes in every case will give the degree of severity.

Discussion

D. A. Pyke (Oxford): How will you define “mild” and “severe” diabetes?

J. Grunnet (Copenhagen): A diabetes 1. which is not inconveniencing the patient too much, 2. with fasting blood sugar never exceeding 0.20 per cent, 3. with no ketonuria and 4. with no insuline-injection is what I call a mild diabetes.

Baker Clinic Research Laboratory, New England Deaconess Hospital
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A FOLLOW-UP STUDY OF CHILDREN OF YOUNG DIABETIC MOTHERS¹

By J. DITZEL, P. WHITE and L. SARGEANT

The advent of insulin and careful prophylactic treatment of diabetes during pregnancy has enabled most young diabetic women to become mothers. All their children are carriers of the disease and an unknown number of them will develop diabetes later in their lives. The etiology and possible protecting or reversing factors in diabetes may be elucidated by studying the natural development of these children.

At the Joslin Clinic children of young diabetic mothers have been examined in order to establish answers to the following questions:

- (1) How great is the incidence of diabetes and what is the natural course of their disease?
- (2) What is their growth and developmental pattern?
- (3) What is the relationship between the accelerated vascular disease in diabetes and the disturbance in the carbohydrate metabolism?

Methods and Results

The results are obtained from repeated examinations in 1953 and 1956 upon a representative group of 100 children of young diabetic mothers. The children were evenly distributed as to sex, and their ages varied initially from 3 to 20 years. The duration of the maternal diabetes at the time of the birth of the child varied from 0-21 years. The age at onset of the maternal diabetes varied from 4 to 36 years.

Three kinds of tests were performed on all the children: (1) glucose

¹ This work was supported by the Massachusetts Lions Eye Research Fund and Public Health Service Grant A-H-1070.

tolerance test, (2) growth and development studies, and (3) examination of their smaller blood vessels.

(1) The quantity of glucose given in the tolerance test depended upon age and body weight. Blood sugar tests were made fasting and at one-half, one-hour and two-hour intervals after giving the glucose. The blood sugar was determined according to the method of Folin-Malmros. The diagnosis of diabetes was made if the child showed glycosuria and the capillary blood sugar rose to 250 mg. per cent or the venous blood sugar rose to 170 mg. per cent or above. The condition was indicated as borderline if the fasting capillary blood sugar exceeded 140 mg. per cent or the postprandial capillary blood sugar varied from 200 to 240.

Among the 100 children examined in 1953, 10 were classified as diabetics and 15 others had glucose tolerance curves classified as borderline. Thus, a total of 25 per cent showed abnormal glucose tolerances. Of the 10 children showing diabetes, 6 are at present on insulin therapy. In the period between 1953-1956, 3 more children spontaneously developed diabetes. The glucose tolerance tests were repeated in 58 of the children in 1956. At this time 2 children showed diabetic curves and 6 other cases showed borderline curves (Table 1). Thus the incidence of diabetes in the offspring of obstetrical diabetics is now in the ratio of 15 in 100. For the general juvenile population the incidence is 1 in 2500 children. The incidence of juvenile diabetes in children of young diabetic mothers is therefore more than 375 times as common than in the case of the general juvenile population. According to the inheritance of Mendelian ratios of the recessive type, there is a calculated risk of approximately 22 per cent developing diabetes in the life span if one of the parents has diabetes. Since the figure determined in this study is now 15 per cent, an increase in this percentage to at least 22 per cent is still conceivable with this type of inheritance. However, 15 per cent is high considering the age of the individuals. Also, another

Table 1. Repeated Glucose Tolerance Tests in 100 Children of Young Diabetic Mothers.

Year	Children (No.)	Diabetic (No.)	Borderline (No.)
1953	100	10	15
1954	—	3	—
1956	58	2	6
Combined incidence		15 (15%)	21
		36%	

20 per cent of the children show borderline glucose tolerances which later may be diabetic in type.

Nine of the original 10 diabetic cases were re-examined in 1956 and 6 still showed diabetic curves, 2 cases had regressed to borderline, and one child now showed a normal glucose tolerance. Similar regressions occurred among the children originally classified as borderline cases. Of the 15 borderline diabetic cases found in 1953, 7 were re-examined and 3 cases were still borderline, while 4 were now normal. Therefore, the disturbance in the carbohydrate metabolism has a dynamic and fluctuating character even at this early stage during which, however, the child has *no* objective or clinical symptoms (i.e., he has a chemical diabetes). Later on the disturbance becomes manifest and insulin therapy is needed.

(2) The growth and development study showed that the children had a tendency to superiority of growth in stature and weight. Thus 57 per cent of the boys and 31 per cent of the girls varied from 3 to more than 10 inches above the *Engelbach* standard of height for age. Eighty per cent of the boys and 66 per cent of the girls were from 5 to more than 50 pounds above the standard weight for height and age. Twenty-five per cent of the boys and 20 per cent of the girls were exceeding normal weight by 30 pounds. When the children were re-examined 3 years later, this result was confirmed. No relationship was found between obesity and the development of diabetes.

(3) The third part of the examination of these children was to determine the extent, if any, of vascular changes. During recent years it has become evident that vascular degeneration is intimately associated with diabetes. The exact relationship is not known. Three possibilities suggest themselves: (1) that the vascular degeneration is a consequence of the disturbance of that phase of the metabolism that is controlled by insulin; (2) that the vascular lesions reflect a still unknown underlying disturbance; (3) that the vascular lesions are due to the inheritance of a "poor" vascular system gene-linked with diabetes. The vascular disease in the juvenile diabetics is mainly a generalized, slowly developing hyalinization of the capillaries and venules. Therefore *in vivo* investigations with a technique which makes possible the observance of the smaller blood vessels on the microscopic level might be valuable to elucidate factors involved in the pathogenesis of the vascular disease. For such purpose the application of the stereoscopic dissecting microscope to the study of the conjunctival vessels has been found suitable. At the Joslin Clinic more than 1200 young diabetic and non-diabetic subjects have been examined with this technique. It has been shown that the smaller blood vessels react to the condition of the disease with excessive vasomotor responses, which mainly consist of arteriolar

constriction and venular distension (fig. 1). These caliber changes of the small blood vessels produce stasis and exudation through the venous part of the capillaries and venules, which after a period of years may lead to the hyalinization of the basement membranes. Since studies of the smaller blood vessels in diabetic children indicated that even with very short duration of the disease vascular changes were present, it was of interest to investigate the children of diabetic mothers for abnormal vasomotor patterns. In 1953 and 1956, 43 per cent and 35 per cent, respectively, of the children showed such vascular pattern changes. The children who exhibited the abnormal vascular responses were predominantly those with hyperglycemic tolerance tests. Among 16 cases who in 1953 showed abnormal vasomotor pattern and had normal glucose tolerance, 3 developed diabetes during the following three years. The investigation suggests that the degeneration of the smaller blood vessels is a consequence of abnormal vasomotor responses and related to the disturbance in the carbohydrate metabolism.

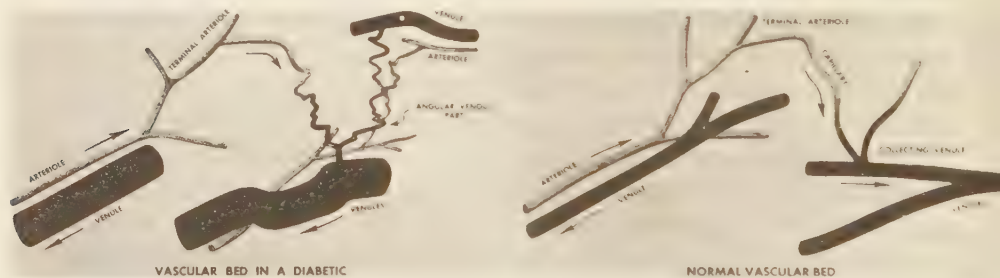


Fig. 1. The vascular bed of a young diabetic as compared to a normal vascular bed.

Conclusion

A follow-up study after a 3-year-period of 100 children of young diabetic mothers showed that they exhibit (1) a high incidence of diabetes (15%), (2) a disturbance in growth and development, the children being taller and much more obese than normal, and (3) a tendency to show an abnormal vascular response.

Even though diabetes in this group was found to be 375 times more common than in the general juvenile population, this incidence is still explainable by inheritance of diabetes according to Mendelian ratios of the recessive type.

Children of diabetic mothers should be examined carefully by yearly glucose tolerance tests to determine the presence or absence of diabetes.

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GÉNÉTIQUE DE L'HÉMOCHROMATOSE

Par M. LAMY, G. SCHAPIRA, J. FRÉZAL et P. MAROTEAUX

Ce travail est fondé sur une enquête familiale et sur l'étude biologique des enfants de 69 malades atteints d'hémochromatose idiopathique.

I. — *L'enquête familiale* a permis de retrouver 3 hémochromatoses certaines chez les frères de 30 malades et quelques pigmentations, diabètes ou cirrhoses isolés chez les ascendants et germains.

Il n'a pas été constaté d'augmentation notable du taux de la consanguinité (1 sur 36).

II. — *La sidérémie.*

1^o *Les résultats:*

La sidérémie a été dosée chez 40 malades ($250,5 \gamma \pm 38,7$ p. 100 c.c.) 38 témoins masculins âgés de plus de 15 ans ($139,9 \pm 38,3$) et enfin chez 67 fils ou filles de malades.

13 fils de moins de 15 ans (âge moyen: 8,5)	$140 \pm 61 \gamma$ p. 100 c.c.
30 fils de plus de 15 ans (25,6)	$197,4 \pm 66$
15 filles de moins de 15 ans (8,8)	$135,1 \pm 55$
9 filles de plus de 15 ans (25,4)	147 ± 26

2^o *Interprétation:*

A. — La sidérémie moyenne des filles n'augmente pas avec l'âge et la proportion des filles hypersidérémiques est sensiblement la même dans les deux groupes de moins et de plus de 15 ans.

La sidérémie moyenne des garçons de moins de 15 ans n'est pas différente de celle des filles de même âge.

En revanche, la sidérémie moyenne des garçons de plus de 15 ans est notablement plus élevée que celle des garçons de moins de 15 ans et que celle des filles de même groupe d'âge et de même âge moyen.

On pourrait donc admettre que l'hypersidérémie n'est pas apparente chez certains sujets en raison de leur jeune âge et que son développement

serait limité chez la fille après la puberté, sans doute en raison de la perte menstruelle.

B. – Dans cette hypothèse, le groupe le plus favorable pour l'analyse génétique est celui des garçons de plus de 15 ans. Nous l'avons comparé aux groupes des témoins et des malades.

La sidérémie moyenne des garçons de plus de 15 ans est intermédiaire à celle des témoins et des malades.

Les différences entre ces sidérémies moyennes sont hautement significatives.

La distribution de fréquence des sidérémies est modale chez les témoins et les malades, mais paraît bimodale chez les « fils ».

La variance de la distribution des fils est significativement plus élevée que celle des deux autres groupes.

Si nous combinons l'échantillon de témoins et celui de malades, nous obtenons un groupe composite ayant la même moyenne et la même dispersion que celui des fils.

Nous pensons donc que le groupe de fils est hétérogène comprenant deux populations de normaux et d'hypersidérémiques.

III. – Le coefficient de saturation de la sidérophiline

Les coefficients moyens ne sont guère différents chez les filles de moins de 15 ans (respectivement 0,46 et 0,47) et chez les garçons de moins de 15 ans (0,51). Ce dernier chiffre est un peu supérieur à celui des témoins pourtant nettement plus âgés (0,42).

Le coefficient de saturation de la sidérophiline chez les fils de plus de 15 ans (0,60) est intermédiaire à celui des malades (0,77) et des témoins (0,42).

L'examen de la distribution de fréquences montre clairement que deux populations existent parmi les fils d'hémochromatosiques, l'une ayant un coefficient de saturation normal, l'autre un coefficient exagéré.

Si nous comparons les résultats des dosages de la sidérémie et ceux du coefficient de saturation de la sidérophiline, on remarque que la moitié des fils de plus de 15 ans ont une anomalie caractérisée du métabolisme du fer.

Ces résultats sont cohérents avec l'hypothèse d'une transmission de l'hémochromatose selon le mode dominant.

Discussion

A. – Il existe un contraste frappant entre les résultats de l'étude biologique et ceux de l'enquête familiale. Ceci pourrait s'expliquer ainsi:

1° L'hémochromatose manifeste une grande prédominance masculine.

Même si la maladie est due à un gène dominant autosomique, les malades naîtront environ une fois sur deux de parents apparemment sains.

2° Le diagnostic clinique n'est porté dans plus de 50 % des cas qu'après 50 ans. A cette date, les parents des malades sont habituellement décédés. Les renseignements anamnestiques sont imprécis. Il est de plus évident que la mort doit survenir non exceptionnellement avant la constitution de la triade révélatrice. De telles conditions favorisent la sélection de pédigrees « d'allure récessive ».

L'abaissement de l'âge du diagnostic consécutif aux progrès des explorations biologiques doit faire apparaître des observations d'hémochromatose confirmée dans deux générations successives. Il en existe en fait trois récentes (*Pirart, Finch, di Matteo*).

B. — L'un des arguments invoqués en faveur de la dominance est l'absence d'élévation du taux de la consanguinité.

Il n'est toutefois pas impossible que l'hémochromatose se transmette parfois selon le mode récessif. Ce pourrait être le cas dans certaines familles issues d'une union consanguine. Il pourrait s'agir d'une forme spéciale d'hémochromatose, la forme juvénile endocrino-hépatomyocardique (*Nussbaumer et coll.*).

Bernheim, M., M. Berger, R. Uzan et J. Chambron: Acta genet. 7, 107-108, 1957

Clinique Médicale Infantile et Laboratoire de Physique de la Faculté de Médecine de Lyon

LE RÔLE DES FACTEURS GÉNÉTIQUES DANS LE DÉVELOPPEMENT DU MYXOEDÈME CONGÉNITAL ATHYRÉOTIQUE

Par M. BERNHEIM, M. BERGER, R. UZAN et J. CHAMBRON

1° Nous avons étudié les familles de 50 enfants atteints de myxœdème congénital athyréotique dans le but de mettre en évidence un facteur génétique à l'origine de cette affection.

2° Les 50 enfants présentaient une insuffisance thyroïdienne sévère qui s'était manifestée très tôt au cours de la vie. Les épreuves à l'iode radioactif nous ont montré une fixation nulle ou très faible de l'iode par la région cervicale et une absence de synthèse de composés organiques iodés. L'épreuve à la thyroestimuline a été négative.

3^o Nous avons trouvé chez les frères des enfants myxœdémateux une mortalité anormalement élevée au cours des premiers mois de la vie. Bien que la cause exacte de la mort n'ait pu être précisée, nous pensons que cette mortalité est due au myxœdème, ce qui explique la prédilection apparente de cette maladie pour le sexe féminin.

4^o La grossesse ayant donné naissance à l'enfant myxœdémateux a presque toujours été normale; en particulier elle ne s'est jamais accompagnée de l'évolution d'une maladie thyroïdienne chez la mère. Elle s'est cependant prolongée au delà du terme normal dans une proportion importante de cas.

5^o Les enfants myxœdémateux avaient un poids de naissance moyen nettement plus élevé que celui des enfants normaux.

6^o La proportion des antécédents thyroïdiens (goitre simple et goitre exophtalmique) dans les familles d'enfants myxœdémateux était significativement plus élevée que dans les familles d'un groupe témoin.

7^o Les pères et mères, cliniquement normaux, des enfants myxœdémateux, présentaient des anomalies de leur fonction thyroïdienne caractérisées par:

a) une fixation thyroïdienne de l'iode radioactif supérieure à la normale;

b) un taux d'iode protéique radioactif dans le sérum, soit faible, soit fort, en valeur absolue;

c) un taux de conversion de l'iode radioactif plasmatique élevé;

d) un taux d'iode protéique stable élevé.

8^o Les frères et sœurs des enfants myxœdémateux présentaient des anomalies du même ordre.

9^o Ces résultats cliniques et biologiques nous font conclure à l'intervention de facteurs génétiques dans le développement du myxœdème congénital.

10^o Le mode de transmission des maladies thyroïdiennes qui nous paraît le plus probable est le suivant:

a) il existe un gène pathologique unique, responsable de la genèse des diverses maladies thyroïdiennes;

b) les sujets homozygotes vis-à-vis du gène unique sont atteints de myxœdème congénital;

c) les sujets hétérozygotes sont atteints de goitre simple ou de goitre exophtalmique ou présentent seulement une anomalie de la fonction thyroïdienne.

11^o Nous pensons que le gène pathologique agit en augmentant la consommation de l'hormone thyroïdienne par les cellules de l'organisme.

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PROTEIN-BOUND IODINE IN RELATIVES OF PATIENTS WITH THYROID DISEASES

By J. MOSBECH, E. D. BARTELS and H. UHRBRAND

The reasons for dysfunction of the thyroid gland are most often obscure. Genetic factors, however, seem to be involved, as family predisposition to Graves' Disease occurs in about 60 % of the cases (*Bartels*), and also cases of myxedema are often accumulated in certain families (i.a. *Møller*).

In trying to explain the etiological factors in congenital myxedema *Uzan* has recently examined relatives of 25 children suffering from this disease, and he arrived at some very interesting findings.

Thyroid diseases were found in 17 of the 25 families examined. Congenital myxedema occurred in 4 families, i.e. one case in a sister of one of the children in question and 3 cases in remoter relatives of the children mentioned. In 13 other families cases of Graves' Disease were found, 5 in mothers of the children with congenital myxedema.

Uzan examined the thyroid function in healthy relatives of patients with congenital myxedema by determination of plasma protein-bound iodine according to *Barker's* method [1951].

Out of 22 relatives examined, 12 persons displayed increased plasma protein-bound iodine values: 13-15 $\gamma\%$. (The range of normal values being 4-10 $\gamma\%$.) This was interpreted to reflect hyperactivity of the thyroid gland in these clinically healthy individuals.

The author concluded from his findings, combined with examinations with radioactive iodine, that congenital myxedema must be hereditary and advanced the hypothesis that thyroid disease should appear under the influence of a dominant gene; heterozygotic individuals, who have only the disposition from one parent, included patients with: struma, Graves' Disease, thyrotoxic adenoma or simply biochemical alterations in the blood, i.e. increased values of plasma protein-bound iodine. In individuals

who received the pathological "gene" from both parents, i.e. homozygotic individuals, the disease would, according to Uzan's hypothesis, appear as congenital myxedema.

In order to throw further light on the question of chemical alterations in the blood in relatives of patients with thyroid disease plasma protein-bound iodine was determined in 22 healthy individuals. These persons were: the parents of 5 patients with congenital myxedema and the parents of 6 patients with Graves' Disease. The patients are all taken from the Københavns Amtssygehus Gentofte's Children's Ward and the Department of Internal Medicine N. The diagnoses are verified according to the usual criteria and only such cases are included in the investigation as were considered to be typical clinically and according to laboratory results.

The method for determination was that described by *Barker* (1948) (our range of normal: 3,9–7,6 $\gamma\%$, average value 5,6 $\gamma\%$). All results of the analyses are mean values of duplicate determinations. As a special control a "recovery"-determination is included in each series of analyses, a specimen of plasma being analysed with and without addition of a certain amount of potassium iodine. The amount of potassium iodine added was refound with an accuracy of $\pm 1 \gamma\%$.

The results appear from the table.

Protein-bound iodine in parents of patients with myxedema and Graves' Disease.

Graves's Disease			Myxedema		
	Fathers	Mothers		Fathers	Mothers
1)	6.2 $\gamma\%$	2.6 $\gamma\%$	1)	4.3 $\gamma\%$	4.1 $\gamma\%$
2)	4.3 $\gamma\%$	5.8 $\gamma\%$	2)	4.4 $\gamma\%$	2.6 $\gamma\%$
3)	3.3 $\gamma\%$	7.1 $\gamma\%$	3)	3.9 $\gamma\%$	6.3 $\gamma\%$
4)	2.7 $\gamma\%$	5.2 $\gamma\%$	4)	3.3 $\gamma\%$	4.2 $\gamma\%$
5)	4.7 $\gamma\%$	4.4 $\gamma\%$	5)	6.3 $\gamma\%$	7.4 $\gamma\%$
6)	2,6 $\gamma\%$	4,1 $\gamma\%$			

It will be seen that 15 out of the 22 individuals examined had values of plasma protein-bound iodine within the stated range of normal values. 3 showed values between 3 and 4 $\gamma\%$, which is within the limit of error of the method, while 4 persons (2 fathers and one mother of patients with Graves' Disease and one mother of a myxedema patient) had values of plasma protein-bound iodine below normal.

In no case did increased values of protein-bound iodine appear, and

thus it has not been possible through the investigations in question to reproduce the findings of *Uzan*.

The importance of the low values of plasma protein-bound iodine found is doubtful. Only a larger material of families of patients with thyroid diseases can decide whether these findings are more than coincidental.

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Discussion

M. Berger (Lyon): Après avoir trouvé, au début de notre travail, des chiffres élevés d'iode protéique chez les parents d'enfants myxoédémateux, nous avons trouvé ensuite des chiffres normaux et même des chiffres bas, de sorte que la valeur moyenne de l'iodémie protidique des parents de myxoédémateux est peu différente de celle des sujets normaux, mais la dispersion est plus grande. Nos résultats sont donc finalement peu différents de *M. Mosbech*. Les chiffres bas d'iodémie protidique joints à la fixation élevée de l'iode radioactif nous paraissent traduire une utilisation rapide de l'hormone thyroïdienne par les tissus. Rappelons que *Ingbar* a montré récemment que la thyroxine radioactive disparaissait plus vite de la circulation chez les parents (cliniquement normaux) de sujets hyperthyroïdiens que chez les sujets normaux.

Carter, C. O. and M. J. Simpkins: *Acta genet.* 7, 111-113, 1957

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THE CARRIER STATE IN SEX-LINKED NEPHROGENIC DIABETES INSIPIDUS

By C. O. CARTER and M. J. SIMPKISS

Sex-linked Nephrogenic Diabetes Insipidus is characterised by polyuria from infancy, which is resistant to pitressin with otherwise normal renal function.

Patients not kept fully hydrated develop mental defect and may die young.

In four families the mothers, mothers' mothers and other female relations who, on genetic grounds, might be heterozygous for the gene responsible for the condition, were examined by a simple urine concentration test. For this the women were asked to drink no water after 7 p.m., pass urine before going to bed at 11 p.m., and collect the first specimen of urine passed in the morning.

It was found that the mean specific gravity of the urine specimens from the mothers and also the mothers' mothers was significantly lower than that of controls. These women formed a homogeneous abnormal group, with no more variation within the group than was found in the controls. The "other female relations" group had a lower mean urine specific gravity than the controls and a higher mean than the mothers and mothers' mothers, but the differences were not significant. On the other hand the variation within this group was significantly greater than within the control group and the distribution suggested that 6 of these women behaved like the mothers and mothers' mothers, and behaved like the controls. Although there is some overlap, it is postulated that a mean specific gravity of 1018 on three morning specimens of urine under the conditions of test differentiates the majority of heterozygotes from women who are not carriers of the gene. Diagnosis on the basis of this urine concentration test agrees well with the genetic analysis of the 4 pedigrees.

The four mothers, two young "other female relations" and one mother's mother were also tested for sensitivity to an injection of pitressin given at the height of a diuresis induced by drinking a litre of water. Although the mean fall in urine output was less than that in controls (the mother's mother was excluded from the comparison as none of the controls were old women) the difference was not significant and one mother responded well to pitressin.

The paper will be published in full in *The Lancet*.

Discussion

H. Forssman (Gothenburg): Dr. Carter's lecture was a very interesting one. Like him, I am convinced that if only we could detect the female carriers of nephrogenic diabetes insipidus in time, we could prevent a small number of children from becoming mentally deficient and another small number from an early death.

Incidentally, I described sex-linked nephrogenic diabetes as far back as 1942 in a Scandinavian medical journal, though I did not use the term "nephrogenic". As regards the urine concentration, I examined three women from the same family and mothers of boys with the disease, that is, three unequivocal carriers. They were all free from spontaneous signs and symptoms. On simple concentration tests of urine, one of them reached

a value of 1.026. In other words, she was normal in this respect. The other two, both young and healthy women, could not concentrate above a specific gravity of 1.014 and 1.019, respectively. The only explanation that could be given for their inadequate power of concentration was that they carried the gene responsible for diabetes insipidus.

It seems, consequently, that the carrier state may sometimes reveal itself in a reduced power of concentration. However, in other cases of known heterozygotism, this sign is not present. In doubtful cases, therefore, a normal power of concentration does not exclude the possibility of the woman being a carrier.

The heterozygotes in families with the other sex-linked form of diabetes insipidus, the one which is not nephrogenic but is ordinarily susceptible to the antidiuretic hormone, sometimes present an interesting effect of the gene they carry. During the last three or four months of pregnancy they develop a full-blown diabetes insipidus syndrome. I have described this phenomenon in several articles. However, I have never heard any carrier of the nephrogenic form relate of this very striking symptom during pregnancy. I have questioned 6 "nephrogenic" carriers who had given birth to 15 full-term babies but none of them had experienced any diabetes insipidus when they were pregnant.

Lamy, M., P. Maroteaux et J.-P. Bader: *Acta genet.* 7, 113-114, 1957

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ÉTUDE GÉNÉTIQUE DU GARGOYLISME

Par M. LAMY, P. MAROTEAUX et J.-P. BADER

Résumé

Le matériel de cette étude est constitué par les observations publiées dans la littérature mondiale, 4 cas personnels et 12 cas inédits.

Une forte prédominance du gargoylisme est trouvée dans le sexe masculin: 91 observations concernent une fille, 178 un garçon.

Une transmission récessive autosomique de la forme féminine peut être affirmée: l'élévation du taux de la consanguinité des parents, l'incidence de la maladie chez les frères et sœurs (étudiée par la méthode de Weinberg) le prouvent. Dans cette forme récessive autosomique il ne semble pas y avoir de différence de pénétrance suivant le sexe car les frères et sœurs de *propositi* sont également atteints.

Chez le garçon existent certainement deux formes: l'une récessive autosomique, l'autre récessive liée au sexe dont 8 pedigrees ont été publiés.

Une tentative de différenciation clinique est faite entre ces deux formes. Si la forme récessive ne diffère nullement chez le garçon et chez la fille, en revanche dans la forme liée au sexe les opacités cornéennes paraissent absentes, l'évolution est moins sévère, le retard statural plus rarement retrouvé, mais la surdité est nettement plus fréquente.

Par diverses méthodes d'estimation la fréquence de cette forme liée au sexe a pu être montrée voisine de 31 %.

Mais certains faits restent difficilement interprétables: diminution du pourcentage des frères et sœurs atteints dans les familles de garçons, plus grande fréquence des cas sporadiques masculins, rareté relative des pedigrees ou la maladie paraît liée au sexe.

L'explication de ces phénomènes est discutée: défaut de pénétrance, phénocopie ou mutation.

Miall, W. E., and P. D. Oldham: Acta genet. 7, 114-120, 1957

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THE INHERITANCE OF ARTERIAL BLOOD PRESSURE

By W. E. MIALL and P. D. OLDHAM

Most of the published work on the inheritance of arterial pressure is based on the assumption that a sharp boundary separates normal from abnormal pressure. The whole concept of essential hypertension as a clinical entity has, however, been doubted by *Hamilton, Pickering, Fraser Roberts* and *Sowry* [1], and we shall be hearing more of their reasons for this from Dr. *Fraser Roberts* in the next paper. I propose to summarise briefly the evidence which they have presented, and then lead on to the results of two studies of arterial pressure and its inheritance which we have undertaken in representative samples of populations in South Wales as a direct sequel to their work.

Hamilton and his colleagues approached the problem from much the same viewpoint as most previous workers, and studied groups of both hypertensive and normotensive propositi and their first degree relatives, and a group of patients taken as representative of the general population to determine gene frequency.

They demonstrated that in the general population the frequency distributions of systolic and diastolic pressure, though not normal in shape, show no evidence of bimodality in any age group; they confirmed that both pressures rise with age, and showed that no natural boundary occurs at the generally accepted figures of 150 systolic and 100 diastolic, or indeed at any other points. They showed also that the relatives of hypertensive propositi had pressures which were higher at all ages than those of normotensive propositi.

A method of allotting blood pressure scores to allow for differences in age and sex was worked out by *Dr. Fraser Roberts* [2] and thus enabled direct comparisons to be made between propositi and relatives of any age and either sex. By using these scores they were able to show that the resemblances between the hypertensive propositi and their parents, siblings and children did not differ significantly, and that the overall regression of relatives' score on propositus's score had values of 0.240 and 0.238 for systolic and diastolic pressures respectively. These regressions differed highly significantly from zero but the corresponding regressions in the case of their normotensive group, which was of smaller numbers, had values which did not differ significantly either from zero or from the values for the hypertensive group.

We determined therefore to see whether these findings were supported in a more representative sample of the general population [3], and chose our propositi by a random method from the total population over the age of 5 years of a South Wales mining valley, the Rhondda Fach, and thus avoided the artificial division of propositi into those with normal and those with abnormal pressure.

Casual arterial pressure measurements were made for 95 per cent of the 261 propositi—a 1 in 90 sample. Similar measurements were made for 98 per cent of the 1005 first degree relatives of these subjects who lived within 25 miles of the valley. Recordings were made after the subjects had been seated for at least five minutes, and as the girth of the arm has been shown by *Ragan and Bordley* [4] and several other workers to influence arterial pressure as recorded by a sphygmomanometer, arm girth measurements were also made for each individual.

Our results confirmed that there was no evidence of a bimodal distri-

bution of arterial pressure in any age group. We used age adjusted blood pressure scores derived in the same way as those of *Hamilton* and his colleagues; these scores show the number of mm. Hg., in units of 5, by which an observed reading exceeds or falls short of the mean for the general population for that age and sex, the scores being further adjusted to allow for the increase of variance with age. Using these scores we also found that a single regression will describe the dependence of systolic pressure of relatives of all kinds on *propositi* of either sex. In our survey we analysed systolic pressure data only as there is a remarkable identity in the results obtained from systolic or diastolic pressure.

The regression coefficient we obtained had the value 0.239, with a standard error of 0.032; this compared extremely closely with that of 0.240 obtained for first degree relatives of hypertensive *propositi* by *Hamilton* and his colleagues [5].

This means, therefore, that if the systolic pressure of an individual at age 60 was found to be 50 mm. Hg. above or below the mean value for that age and sex, the mean value of his or her first degree relatives would be expected to be 12 mm. Hg. above or below that value at the same age.

We were, however, struck by three other observations. Firstly, in many of the families studied, within any one family the variation in blood pressure seemed to be very often explicable in terms of arm girth, a measurement which is highly correlated with weight; secondly, below the age of 45 in both sexes there was a remarkable similarity between the curves relating systolic pressure with age and arm girth with age, as shown in Fig. 1; and thirdly, when we derived age-adjusted arm girth scores and compared the scatter of the regressions between *propositi* and their relatives for arm girth and for systolic pressure about their mean values, there was a remarkable degree of resemblance between the two, as shown in Fig. 2. This resemblance was closest where the relationships involved *propositi* and relatives of the same sex, and less marked when *propositi* and relatives were of different sexes.

These observations led us to wonder if the inheritance of arterial pressure might be entirely explicable in terms of arm girth or weight, and whether, if we derived scores allowing for both age and arm girth, the inheritance factor might disappear completely. Our data, however, were inadequate to allow us to do this at that time, and as in any case we wanted to investigate environmental influences, an exactly comparable survey was carried out early this year in a random sample of the population living in the Vale of Glamorgan, a predominantly agricultural area only about fifteen miles distant from the mining valley.

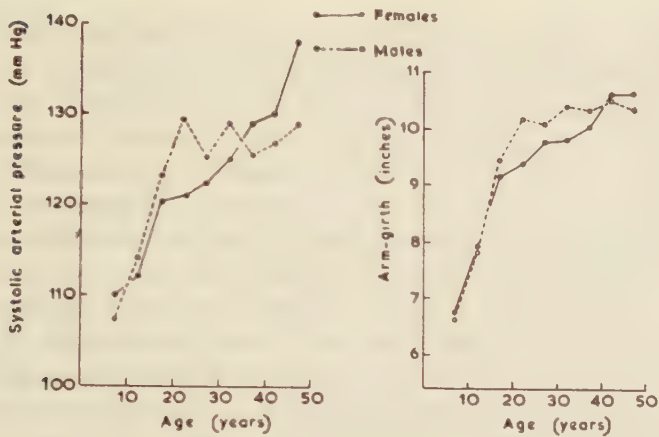


Fig. 1. The relationship between systolic pressure and age, and arm-girth and age. Rhondda Fach propi and relatives under the age of 50 years.

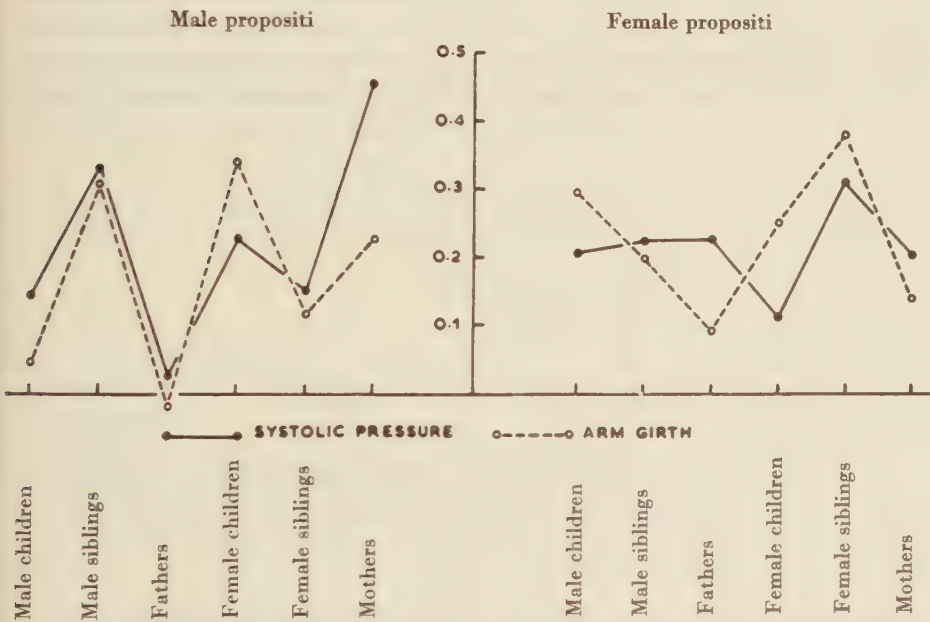


Fig. 2. Regressions of (a) systolic pressure and (b) arm girth of relatives on propi.

In this new survey we again saw over 95 per cent of 390 propi and over 95 per cent of 1316 first degree relatives living within 25 miles of the area.

The mean values for systolic pressure at different ages for both male and female propositi were remarkably similar in the mining and the rural areas and the fitted regressions were not materially different, so we decided to pool the data from the two surveys and calculate new age-adjusted scores, based on the average of these regressions, and also scores to allow for both age and arm girth. The former were derived in an exactly comparable manner to that already described. For age and arm girth adjustment we are indebted to our colleague, Dr. *M. E. Wise*, for his analysis from which scores were derived. *Wise* confirmed that below the age of 37 in females and 45 in males no adjustment for age was necessary if allowance was made for arm girth. Above those ages the blood pressure, after correction for arm girth, increases with age by an almost constant proportion; the percentage increase from year to year has a value of 1.4 for females and 1.2 for males.

With this survey we have been able to confirm and extend the results of the previous one. In Fig. 3 we have plotted mean systolic pressure scores of relatives against scores of propositi. This is now based on 620 propositi and over 2300 relatives, and the scatter of these means about the regression line, which now has a coefficient of 0.224 with a standard error of 0.022, is no more than would be expected by chance.

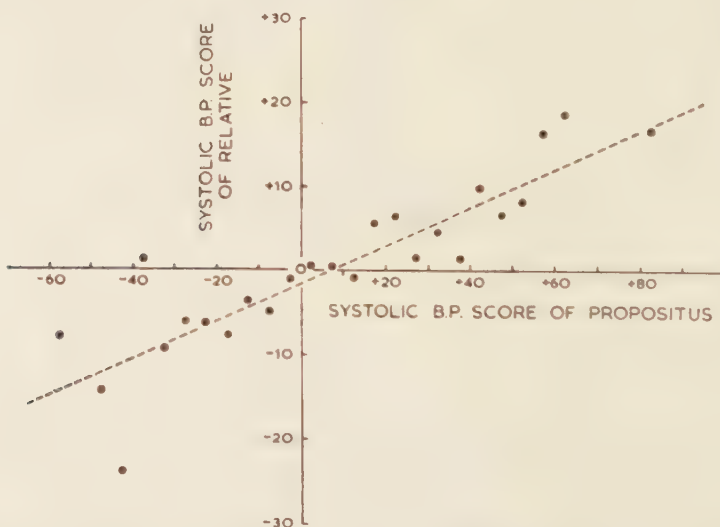


Fig. 3. The relationship between the systolic blood-pressure scores of propositi and the mean systolic scores of relatives.

We conclude with confidence, therefore, that the resemblance between relatives and propositi is similar at all ranges of arterial pressure.

When we came to analyse the regressions of relatives on propositi for our two types of score we were considerably surprised to find that the pattern of inheritance was not only not diminished but actually slightly enhanced by allowing for arm girth. For all relatives on all propositi the average regression for age adjusted scores in different groups now has the value 0.22, and for age and arm girth adjusted scores it has risen, though almost certainly not significantly, to 0.24.

In summary, therefore, we confirm the findings of *Hamilton* and others that there is no evidence to suggest that essential hypertension presents anything more than one end of a continuous distribution of arterial pressure which is much influenced by both age and arm girth or weight. It appears, therefore, to be no more reasonable to talk of essential hypertension than essential obesity; this, of course, is not to deny that both hypertension and obesity are associated with increased risks. We have also demonstrated that the resemblance between propositi and relatives is independent of the range of arterial pressure considered, and that allowance for arm girth makes little difference to this genetic effect.

Finally we would like to stress what *Hamilton* and his colleagues have pointed out, that even "a modest degree of genetic resemblance can produce a striking association when the dividing line between normal and abnormal is drawn at a level near to that ultimately attained by the average person".

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5. *Hamilton, M., G. W. Pickering, J. A. Fraser Roberts and G. S. C. Sowry: Clin. Sci. 13, 273, 1954.*

Discussion

B. Lindegård (Lund): In a preliminary study on 60 adult Swedish male siblings (20–30 years old) I have found an intra-pair correlation concerning the systolic as well as the diastolic blood-pressure. Though there was a fairly close association between blood-pressure and the amount of body-fat, the latter variable did not show any correlation between the siblings. The muscularity, recorded as the gross muscular strength, did not show any correlation with the blood-pressure, nor between the siblings.

The correlation between the arm-girth and the blood-pressure should therefore presumably be a result of the fatness alone.

I would like to ask Dr. *Miall* if this is in line with his opinion.

W. E. Miall (Cardiff): In future investigation on this point we should take the arm-girth in consideration and try to eliminate its influence on the results by performing partial correlation calculations.

Fraser Roberts, J. A.: Acta genet. 7, 120, 1957

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THE GENETICS OF ESSENTIAL HYPERTENSION

By J. A. FRASER ROBERTS

This paper was an addendum to that of Dr. *Miall* and Mr. *Oldham*, who included a summary of results already published by Professor *Pickering*, Dr. *Sowry*, Dr. *Hamilton* and myself. The paper read was largely a commentary on lantern slides, so an abstract is given here.

The original work was chiefly concerned with two samples of measurements of arterial pressures, (1) 2,000 out-patients attending dermatological, orthopaedic clinics etc., called the "population sample". (2) 1,000 first degree relatives of hypertensive subjects, who included a large number recorded in full in a monograph by Dr. *Soby*. As is always found, the frequency distributions were distinctly non-normal, showing marked positive skewness and marked positive kurtosis, making it somewhat difficult to decide about the presence or absence of bimodality.

Re-examination of the figures has shown that the frequency distributions of the two samples, including both systolic and diastolic pressures, are very closely normal when the units of measurement are transformed to a logarithmic scale. It has been pointed out, notably by *Gaddum*, that most biological measurements tend to be more normally distributed on a logarithmic scale than on a linear scale. Hence the present examination of the figures supports the conclusion that there is no evidence of bimodality, and strengthens the theses, first, that essential hypertension is no more than the positive end of the normal distribution of arterial pressures in the population and, second, that the genetic element in hypertension is no more than the tendency for relatives to resemble each other in pattern of arterial pressure—a tendency which is quantitatively the same at all levels from highest to lowest.

The full details of this work will be published in *Clinical Science*.

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HEREDITARY ACROMELALGIA (OR "RESTLESS LEGS"?)

By J. HUIZINGA

A few years ago a fisherman incidentally told us about peculiar paraesthesiae in his feet, occurring usually shortly after he had gone to bed, but also when the legs had been kept still for a while (on visits, in the cinema, etc.). During such attacks he nearly always found it impossible to resist fidgeting with his feet or kicking against the legs of his chair. When in bed, he would try to get some relief by pushing away the bedclothes and sticking out his feet. When the peculiar feeling still did not disappear he usually got out of bed to put his feet under the tap. When on his fishing-boat he used to leave his bed either to fill a bucket with seawater to "cool" his feet or to walk up and down the cold deck. He could not be certain that once he was asleep he would not be reawakened by these "crawling" sensations.

It appeared to be impossible to define the paraesthesiae. "It is not a pain", he said, "but something happens deep inside". No objective evidence of disease to be connected with the symptoms mentioned could be found in this patient. As far as the diagnosis is concerned, the fact that this patient instinctively seeks to provoke a vasoconstriction in the way described points to *Tinels's* "nocturnal acromelalgia" [1937, 1939]. The typical behaviour of the patients to calm down the crisis is depicted in nearly all descriptions: "...ils marchent pieds nus sur des carreaux, ils entourent leurs mains douloureuses des linges imbibés d'eau froide, ils s'installent dans leur lit, jambes pendantes hors des couvertures et même des draps" (*Broustet* [1948]), or "The patients are forced to lie and move their feet about, hold them outside the bedclothes, cool them on a stone floor or the like, or walk up and down" (*Ekbom* [1945]).

On the other hand, the fact that our patient could not possibly describe the feeling during an attack and the irresistible urge to move his

legs when the paraesthesiae are present clearly point to the diagnosis "restless legs". This name perfectly characterizes "asthenia crurorum paraesthetica" (anxietas tibiarum), described by *Ekbom* [1945, 1950, 1951], and was coined by this rediscoverer of that "disease". The numerous case histories given by *Ekbom*, however, never point to the typical significance of cold as described above and, moreover, the feet appear to be seldom involved in "restless legs". In the third place, the asthenia (described as a "weak and tired feeling" in the legs of many of his patients) is absent in our case. This latter case appears to exhibit a mixture of symptoms of both acromelalgia and "restless legs". In "restless legs" *Ekbom* found hereditary factors of definite importance. His data were not collected with a view of analysing the probable significance of heredity, yet many of his patients had (near) relatives with a similar complaint.

It would not have been necessary to dwell on the differences and similarities in symptomatology of *Ekbom*'s "disease" and that present in our case, if the complaints of our fisherman were not those of many of his relatives. The pedigree, comprising some 200 members to date shows the character to be a perfectly regular dominant: any person affected possesses one parent with the same syndrome and about half of the total offspring of persons affected appears to be also affected. Males and females are equally affected. Our data goes back 5 generations. In some patients the complaint has been present from their school years onwards ("restless legs" is mainly manifested in adult age; acromelalgia is stated to have a predilection for elderly people); the chronic nature of the condition is mentioned by some patients over 80 years of age.

Of particular importance may be the fact that a sister of our *propositus* probably does not suffer from the disease present in her brother but from acroparaesthesia: an intermittent paraesthesia in the fingers which a.o. urges the patient to rub the hands in a characteristic way.

It should be considered that the three rather similar syndromes (asthenia crurorum paraesthetica, acroparaesthesia and "nocturnal" acromelalgia) are genetically linked. Clinically there are several points of similarity in these syndromes, as mentioned by *Ekbom* [1945].

For the time being we have chosen the name "acromelalgia" to designate the present hereditary syndrome, as in our opinion the "acromelalgic" part of the case histories has proved to be of definite diagnostic value. The localization in the feet (though not exclusively), together with the absence of asthenia would make it a too atypical "asthenia crurorum paraesthetica". In the second place this choice of name may provoke re-investigation of the relationships between the three syndromes mentioned.

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Ekbom, K. A.: Acta med. scand., suppl. No 158, 1945. Acta med. scand., suppl. No 246, 64-69, 1950. Svenska Läkartidn. 48, 862-872, 1951.
Tinel, J.: Le système nerveux végétatif, Paris 1937. Progr. méd., Paris, 18, 826, 1939.

Discussion

J. G. Y. de Jong (Heerlen): Has Dr. *Huizinga* looked in his patients for achylia gastrica and calcium contents of the blood?

Especially achylia gastrica may be hereditary and may give rise to paraesthesia.

J. Huizinga (Utrecht): 1. Gastric juice: presumably normal. 2. Serum calcium: not investigated.

Adlersberg, D.: Acta genet. 7, 123-124, 1957

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GENETIC ASPECTS OF ATHEROSCLEROSIS

By D. ADLERSBERG

Two inborn errors of lipid metabolism show a close relationship to atherosclerosis: idiopathic hyperlipemia and idiopathic hypercholesteremia. Although both abnormalities resemble each other in this respect, there are distinct clinical and biochemical differences between them.

The study comprised twenty families and five additional persons with idiopathic hyperlipemia (total 89 persons) and 77 families and 49 additional persons with idiopathic hypercholesteremia (total 390 persons). Coronary atherosclerosis was present in 34 % of the persons of the first group and in 43 % of persons of the second group. Xanthomatosis in idiopathic hyperlipemia was usually of the tuberosum type while that seen in idiopathic hypercholesteremia was of the tendinosum variety. Both errors of lipid metabolism were encountered more frequently among men than women. The preponderance of men was more pronounced in idiopathic hyperlipemia (65 %) than in idiopathic hypercholesteremia (57 %).

Among close blood relatives of patients with idiopathic hyperlipemia, this error of lipid metabolism as well as that of idiopathic hypercholesteremia was seen. The study of the "mixed families" suggested that both disorders may be genetically and perhaps biochemically closely related and may perhaps be similarly transmitted by a dominant trait with incomplete penetrance.

The biochemical differences between the two metabolic disorders included chemical analyses of serum lipid partition, electrophoretic studies of serum lipoproteins, changes of serum lipids and lipoproteins after heparin and metabolic studies of exogenous and endogenous cholesterol metabolism with the help of isotopes.

Grebe, H.: Acta genet. 7, 124–127, 1957

Frankenberg-Eder, Deutschland

ZWERGWUCHS ALS GENETISCHES PROBLEM

Von H. GREBE

Am Beispiel des Symptoms «Zwergwuchs» – nicht bei menschlichen Zwergwuchsrassen, sondern bei pathologischen Zwergwuchsformen innerhalb von Populationen mit höherer Durchschnittsgröße – wird gezeigt, wie groß die Zahl pathologischer Gene sein kann, die zu menschlichen Körperformveränderungen führen können.

Besonders wird Wert auf die Feststellung gelegt, daß vor einer Genanalyse in der menschlichen Erbpathologie eine möglichst weitgehende klinische und pathologisch-anatomische Differentialdiagnose durchgeführt werden muß.

Beim pathologischen menschlichen Zwergwuchs kann die Ursache der Wachstumsstörung in erster Linie in systematisierten Erkrankungen im Bereiche des Skelettsystems (namentlich mit Verkürzung der langen Röhrenknochen der Gliedmaßen), den sog. Systemerkrankungen, beruhen. Die durchweg erbbedingten Systemerkrankungen mit ausgesprochenem Zwergwuchs und geringerer Wachstumsverminderung lassen sich in folgende Gruppen aufteilen:

A. Mit Zwergwuchs einhergehende Erkrankungen des Skelettsystems

1. Proportionierte Zwergwuchsformen.
 - a) Echter (primordialer) Zwergwuchs.
 - b) Hanhart'scher Zwergwuchs.
 - c) Hypophysärer Zwergwuchs.
 - d) Infantilistischer Zwergwuchs.
2. Disproportionierte Zwergwuchsformen.
 - a) Chondrodysplasie.
 - b) Unvollkommene Knochenbildung (Osteogenesis imperfecta, Osteopsathyrosis).
 - c) Dysostotische Zwergwuchsformen (enchondrale Dysostosen).
 - d) Mit Zwergwuchs einhergehende «seltene Systemerkrankungen».

B. Erkrankungen des Skelettsystems ohne (ausgesprochenen) Zwergwuchs

1. Störungen der Knorpelverknöcherung.
 - a) Chondrohypoplasie.
 - b) Multiple Epiphysenstörungen (enchondrale Dysostosen) ohne Zwergwuchs.
 - c) Arachnodaktylie (Marfan-Syndrom).
 - d) Akrocephalosyndaktylie.
 - e) «Seltene Systemerkrankungen» ohne Zwergwuchs.
2. Entwicklungsstörungen anderer Skelettabschnitte.
 - a) Dysostosis cleidocranialis.
 - b) Multiple cartilaginäre Exostosen und Ekchondrome.
 - c) Marmorknochenkrankheit (Osteopetrosis).
 - d) Periostale Hyperostose.
 - e) Osteopoikilie, Melorheostose.
 - f) Ostitis deformans (Paget).

Bei den Erkrankungen der Gruppe A herrscht Zwergwuchs gleichsam als Leitsymptom vor, während bei den Erkrankungen der Gruppe B, je nach dem Betroffensein der langen Röhrenknochen und der allgemeinen Körperentwicklung, auch Wachstumsverminderung bis zu Zwergwuchs vorhanden sein kann.

Von den meisten Systemerkrankungen sind heute verschiedene Erbtypen bekannt. Heterogenie darf deshalb als Regel angenommen werden.

Neben ausgesprochen systematisierten Skeletterkrankungen mit Zwergwuchs können auch mehr auf die Gliedmaßen beschränkte Formen von Mikromelie, Peromelie bis zur Amelie und periphere Wachstumsver-

minderungen in Richtung auf Brachydaktylie mit Wachstumsverminderung bis zu Zwergwuchs verbunden sein. Auch bei diesen Formen sind heute unterschiedliche Erbtypen bekannt, die Heterogenie wahrscheinlich machen. Als weitere wichtige Gruppe pathologischer menschlicher Zwergwuchsformen dürfen die sog. Speicherkrankheiten (Cystinspeicherkrankheit oder Aminoacidurie, amaurotische Idiotie, Niemann-Pick-Krankheit u. a.) mit teilweise fließenden Übergängen zur Gruppe der dysostotischen Zwergwuchsformen zusammengefaßt werden. Den Speicherkrankheiten liegt eine Stoffwechselanomalie zugrunde, durch die es zu Gliedmaßen- und Wirbelsäulenverkürzung neben Speicherung in den verschiedensten inneren Organen kommt. Die großen differentialdiagnostischen Schwierigkeiten innerhalb dieser Gruppe können auch bei der Abgrenzung gegenüber den dysostotischen Zwergwuchsformen mit den zentralen Krankheitsbildern Dysostosis Morquio und Dysostosis Pfaundler-Hurler bestehen.

Rezessiver Erbgang ist bei allen hier einzuordnenden Krankheitsbildern die Regel. Doch darf ebenso bei den einzelnen Krankheitsformen mit Heterogenie (z. B. Pfaundler-Hurler-Krankheit) gerechnet werden.

Zu menschlichem Zwergwuchs können auch – abgesehen von selteneren Systemerkrankungen wie der sog. Chondrodystrophia calcificans congenita oder dem sog. Turner-Kieser-Syndrom u. a. – Krankheitsbilder führen, bei denen neben Zwergwuchs als zweites Leitsymptom Polydaktylie besteht.

Zu nennen ist hier das meist einfach rezessiv erbliche Ellis-van-Creveld-Syndrom mit verwandten Erkrankungen, aber auch zwergwüchsige Formen von Bardet-Biedl-Syndrom oder die von *Laurence-Moon* beschriebene Sippe.

Schließlich können bekanntlich die verschiedensten hormonellen Störungen zu Zwergwuchs führen (thyreogene Zwergwuchsformen) oder Stoffwechselstörungen Zwergwuchs auslösen, die teilweise mit den Speicherkrankheiten verwandt sind (sog. renaler Zwergwuchs oder renale Rachitis, Zwergwuchs-Sonderform von *Debré-Fanconi*) oder von den dysostotischen Wachstumsstörungen als Formen mit Blutbild- und Stoffwechselanomalien besonderer Art abzugrenzen sind.

Zählt man die zusammengetragenen menschlichen Wachstumsstörungen mit mehr oder weniger ausgesprochenem Zwergwuchs, die bis heute bekannt geworden sind, zusammen, so ist eine Mindestziffer von 50–60 Möglichkeiten pathologischer Zwergwuchsbildung beim Menschen nicht zu hoch gegriffen.

Da außerdem bei der Mehrzahl aller angeführten Zwergwuchsformen schon heute Anhaltspunkte für das Zustandekommen durch zwei (manchmal auch mehr) voneinander unabhängige Gene gegeben sind, so darf nach

dieser Heterogenie schon heute festgestellt werden, daß mindestens 100 (wahrscheinlich mehr) verschiedenartige, voneinander unabhängig monomer erbliche Gene krankhaften Zwergwuchs beim Menschen auslösen können. Es gibt deshalb das Beispiel «pathologischer Zwergwuchs beim Menschen» ein eindrucksvolles Bild von der großen Zahl krankhafter Gene und ihrer Wirkungsmöglichkeiten, mit denen wir in der menschlichen Erbpathologie zu rechnen haben.

Taillard, W., A. Prader et R. Tobler: Acta genet. 7, 127-131, 1957

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LE RACHITISME HÉRÉDITAIRE RÉSISTANT À LA VITAMINE D (DIABÈTE PHOSPHORÉ)

Par W. TAILLARD, A. PRADER et R. TOBLER

Cette maladie, longtemps considérée comme une rareté s'est révélée à la suite de recherches récentes comme relativement fréquente, puisque, à la clinique orthopédique et à la clinique infantile de Zurich nous avons pu en observer 18 cas en 4 ans et que Swoboda à Vienne en a réuni également une douzaine de cas en quelques années.

Ce rachitisme fait partie du grand groupe de lésions ostéomalaciques accompagnant une affection viscérale: rachitismes rénaux, hépatiques, syndrome de Fanconi, syndrome de Lightwood-Albright, etc... Il présente cependant des caractères très particuliers qui le distinguent nettement des autres formes de rachitismes viscéraux et qui en font une entité nosologique très clairement déterminée.

Du point de vue clinique, il s'agit d'un syndrome classique de rachitisme grave et floride. Les malades présentent l'aspect typique du nain rachitique à jambes courbes, à pieds plats, à front haut et bombé avec des épiphyses élargies, un chapelet costal, etc. ...

L'image radiologique est également celle d'un rachitisme floride, elle est particulièrement nette au niveau des genoux. On observe comme dans le rachitisme carentiel un élargissement des lignes épiphysaires dont les

limites sont floues, une déformation des métaphyses en pagode ou en coquetier; les trabécules osseuses sont épaissies donnant à l'os un aspect grossier, mal équarri. Les diaphyses sont incurvées, présentant du côté de la concavité un net épaississement de la corticale. Les hanches sont le plus souvent déformées en coxa vara, le thorax est aplati et évasé.

L'image sérologique, biochimique, de la maladie est encore celle d'un rachitisme classique:

Le taux du calcium est normal,
celui du phosphore est fortement abaissé
et celui des phosphatases alcalines est augmenté.

L'azote résiduel, l'urée sanguine, la protéinémie sont normaux.

Contrairement aux autres formes de rachitisme viscéraux, l'examen des urines donne des résultats tout à fait normaux. L'élimination du calcium n'est pas augmentée (le test de Sulkowitch est négatif). Il n'y a pas d'albuminurie, pas de glucosurie, ni d'élimination anormale d'acides aminés.

Par contre l'élimination du phosphore est anormale. Tout se passe comme si le phosphore filtré au niveau du glomérule n'était pas réabsorbé au niveau du tubule rénal et passait dans l'urine provoquant l'abaissement de la phosphatémie. *Fanconi*, mettant ce trouble de l'élimination du phosphore en parallèle avec le trouble de l'élimination du glucose dans le diabète sucré, a baptisé cette forme «*diabète phosphoré*». En faveur de cette interprétation parlent les valeurs très élevées de la clearance du phosphore.

Les images clinique, radiologique, et biologique de la maladie sont donc celles d'un rachitisme tout à fait classique. Cependant, ce rachitisme présente 3 caractères propres qui le différencient de façon très nette du syndrome dû à une carence en vitamine D.

Premièrement: Il ne réagit absolument pas aux doses ordinaires de vitamine D (2000 à 10 000 Unités/jour). Par contre, il réagit lentement et mal à des doses énormes (50 000 à 100 000 Unités/j.). Mais, si les symptômes radiologiques et biologiques s'améliorent au cours du traitement, ils réapparaissent dès que l'on arrête l'administration de la vitamine. Les malades doivent être traités pendant toute leur croissance.

Deuxièmement. La maladie évolue de façon tout à fait particulière. Les premiers symptômes apparaissent en général entre la première et la deuxième année avec les premiers pas et la station debout prolongée. Les déformations des membres augmentent avec la croissance et, si on les corrige par une ostéotomie, elles récidivent.

Il est intéressant de noter que les déformations ne se font pas obligatoirement en varus mais peuvent, selon les conditions mécaniques dans lesquelles se trouve le membre, se faire en valgus, flexus ou recurvatum.

La maladie se stabilise à la fin de la croissance, laissant chez l'adulte des déformations plus ou moins sévères. Le taux du phosphore sanguin reste nettement abaissé, alors que celui des phosphatases est à la limite supérieure de la normale.

Troisièmement. La troisième particularité du rachitisme résistant à la vitamine D est son caractère héréditaire.

En effet, tous les auteurs qui ont étudié ce syndrome insistent sur le caractère familial des lésions. Ainsi *Sivoboda* publie un arbre généalogique où un père transmet le syndrome à 4 de ses filles légitimes et à une fille illégitime qui le transmet à son tour à son fils et sa fille. *Lesne*, *Baage*, *Christensen*. *Petersen* et *McCarroll* publient des arbres généalogiques de transmission de père ou de mère à fils et à fille. La maladie n'est donc pas liée au sexe.

McCune publie deux cas de sœurs jumelles univitellines présentant un syndrome typique. *Kaplan* par contre observe l'atteinte d'un seul de deux jumeaux dizygotiques.

Dans la littérature on relève environ 100 cas publiés avec parmi eux 19 familles présentant une transmission dominante très nette.

Nos propres cas se groupent en 8 familles.

Dans 5 d'entre elles on peut observer une transmission selon le mode dominant tout à fait classique. Mais dans les trois autres les individus malades semblent isolés. S'agit-il d'un mode de transmission tout à fait différent et de type récessif? Faut-il invoquer une dominance incomplète avec une pénétrance très faible du gène dans certaines familles? S'agit-il plutôt d'une expressivité variable, les porteurs de gène capables de transmettre la maladie ne présentant que des symptômes si minimes qu'ils échappent à l'examen médical?

L'étude des cas de la famille Mein (Fig. 1) donne la solution du problème. Le rachitisme résistant à la vitamine D s'est transmis de façon dominante typique dans la plupart des mariages, tous les cas présentant le syndrome complet tant au point de vue clinique qu'au point de vue radiologique et sérologique.

Seule une fille (*Trudy*) fait exception. Elle est cliniquement et radiologiquement saine, cependant elle a transmis la maladie à l'un de ses deux fils qui présente lui aussi le syndrome au complet. Or, lorsque l'on contrôle le taux du phosphore, du calcium et des phosphatases dans le sang de la mère, on trouve une hypophosphatémie très nette (1,9 %) ainsi qu'une légère augmentation des phosphatases comme on peut l'observer chez les adultes présentant les symptômes cliniques et radiographiques de la maladie.

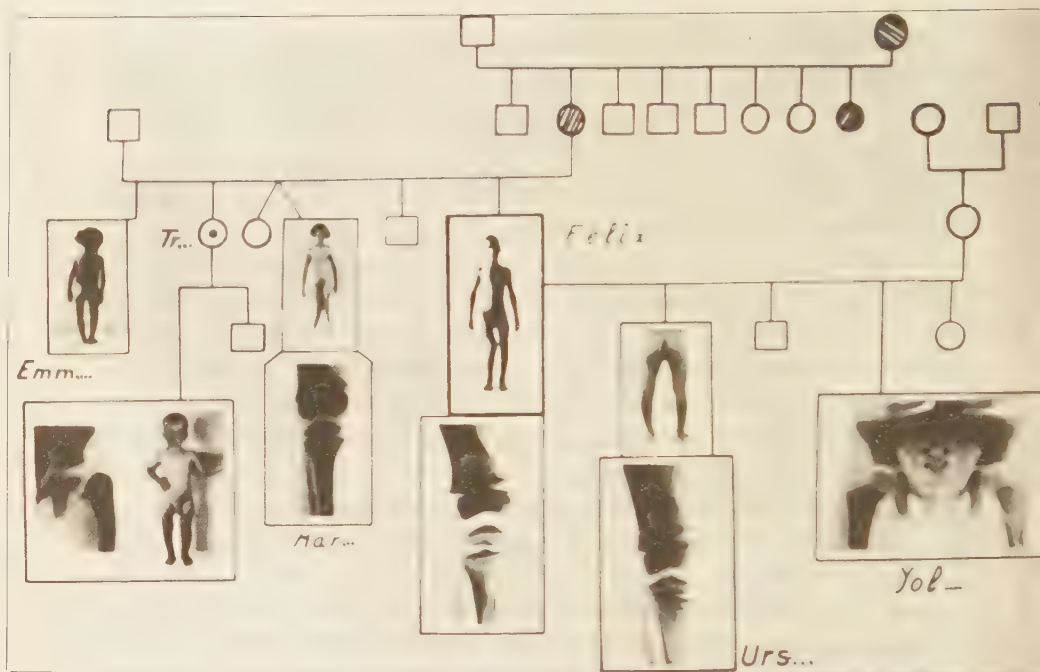


Fig. 1

L'examen sérologique nous permet donc de déceler les porteurs de gène apparemment sains mais capables de transmettre la maladie à leur descendance. Il s'agit d'une simple différence d'expressivité du gène présent dans le patrimoine héréditaire. Ces variations de l'expressivité sont bien connues et on été maintes fois mises en évidence dans des familles où se trouve un gène dominant mais où la transmission de ce gène présente parfois un «saut» inexplicable.

Citons les troubles du métabolisme du chlorure de Sodium dans la descendance de cas de diabète insipide (*Fanconi*), les anomalies de la lipémie chez les membres d'une famille, comptant plusieurs cas de maladie de Nieman-Pick, les troubles électroencéphalographiques dans la parenté d'épileptiques etc. ...

Ces différences de l'expressivité d'un gène sont certainement très répandues, mais elles ne peuvent être mises en évidence qu'au prix de recherches très minutieuses. Cependant, convenablement recherchées et analysées, elles permettent de déceler chez des sujets apparemment sains des microsymptômes servant à établir le mode exact de la transmission

héréditaire et à formuler un pronostic précis pour les différents membres de la famille atteinte.

En résumé, le rachitisme résistant à la vitamine D se présente comme une lésion du tubule rénal entraînant un trouble de l'élimination du phosphore (Diabète phosphoré), mais laissant intacte celle du glucose, des autres sels ou des acides aminés. Cette anomalie du métabolisme du phosphore se traduit par un syndrome clinique, radiographique et biochimique de rachitisme grave résistant aux doses ordinaires de vitamine D évoluant durant toute la croissance et laissant chez l'adulte des séquelles plus ou moins sérieuses.

Ce syndrome est déterminé par un gène autosomique dominant dont l'expressivité est variable. Des individus apparemment sains en peuvent être porteurs et le transmettre à leur descendance. Ces individus peuvent être repérés par le dosage de leur phosphatémie.

Une étude complète de ce syndrome paraît dans *Helvetica Paediatrica Acta* Vol. 11, p. 209, 1956.

Codounis, A.: Acta genet. 7, 131-140, 1957

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A GENETIC STUDY ON THE "HEREDITARY METHAEMOGLOBINAEMIC CYANOSIS" (H.M.C.)

By A. CODOUNIS

There is no doubt that the Hereditary Methaemoglobinaemic Cyanosis (H.M.C.), as a separate morbid entity, is a well defined genetic disease of the red blood corpuscule. This is proved definitely by the great number of publications which appeared from 1946, that is, since we isolated this disease from the other cyanotic disorders and we determined the clinico-biological features of the syndrome.

The total number of cases of H.M.C., published up to February 1946, reached 106, including our own 24 instances of Cyanosis. At the same time, a complete genetic study of eight genealogical trees was made (Table A).

Table A. Demonstrating the complete genealogical trees of the "H.M.C." published since 1946:

A. G. Nationality	Age	Fratries	Members	Cyanotic	Men	Women	Way of trans- mission of the morbid trait	Method of deter- mination of met-HB	Amounts of met-HB in gr. ‰	Met-HB % of total HB	Date of publica- tion	Writers
(1) Hellenic (Greek)	6-80	IV	103	14	8	6	Dominant	Spectroscopic		25-30	1946	<i>Codounis, Loucatos, Loutsides, tree of "Vafthoularis"</i>
(2) German	39-84	IV	22	8	6	2	Dominant	Spectroscopic		11-24	1948	<i>Horlein and Weber</i>
(3) Hellenic (Greek)	6-80	V	85	10	4	6	Dominant	Spectroscopic		18-40	1949	<i>Codounis, Loucatos, Loutsides, tree of "Melaniarides"</i>
(4) French	8-85	V	21	7	2	5	Dominant	Spectroscopic			1949	<i>Lutembacher's tree</i>
(5) Hellenic (Greek)	8-75	IV	26	7	5	2	Dominant	Spectroscopic		10-52	1950	<i>Zacopoulos Tree of Tripolis</i>
(6) Hellenic (Greek)	23-70	III	26	11	5	6	Dominant	Spectroscopic		10-52	1950	<i>Zacopoulos Tree of Ptolemais</i>
(7) Canadian	16-35	IV	33	15	9	6	Dominant	Spectroscopic	1,9-3,2	15-24	1950	<i>Baltzan and Sugarman</i>
(8) German	18-22	V	18	9	4	5	Dominant	Spectroscopic		9,9-36,3	1954	<i>Recknagel and Horlein</i>

The above number of cases proves that the "H.M.C." is not as rare as had been assumed until 1945, when our knowledge concerning this disease was incomplete. It is our opinion that to the above number of 106 we must add the 21 cases published between 1844 and 1945, because we believe that they are also cases of "H.M.C.". As it is known, the trees of those 21 instances were not investigated. So we arrive at the number of 127 instances of "H.M.C.", which we collected from the international literature, hoping that we have not overlooked any case published to date.

Although the vast majority of the authors who have been occupied with the subject after us, agree with us, as far as the clinical, biological and nosologic features of the syndrome are concerned, in the question of the genetic, some of them express objections, maintaining that the tare morbid, possibly, is not transmitted exclusively by the dominant, but by the recessive character, as well.

The purpose of the present paper is to eliminate the doubts and objections. Our experience derives from the recent observations and the genetic study of eight complete genealogic trees, which have been published to date, proving once more that the disease is transmitted by the dominant character. We have taken this stand since we published the generation of "Vaftochilari" (1946).

Since 1939 *Lian*, *Frumusan* and *Sassier* published an excellent piece of work at the Medical Soc. of Paris. In their observation related to two brothers suffering from congenital and familial intracorpuseular methaemoglobinaemia, they perceived the probable inheritance of the disease, but they did not draw definite conclusions on this particular question, as they themselves admit, because their study was limited to only one generation.

Seven years later, *Sivers* and *Ryon*, although they could have used the 19 cases out of the 21 they had mentioned of the international literature, published between 1844 and 1945, commenting on them they characterised the illness as idiopathic congenital methaemoglobinaemia.

In 1946, relying especially on the investigations which we have made with my associates, *Loucatos* and *Loutsides*, in 14 cases of methaemoglobinaemic cyanosis of the same genealogic tree, we have demonstrated definitely for the first time the hereditary mode of transmission of congenital and familial methaemoglobinaemic cyanosis. At the same time, we completed the study of its clinical, biological and therapeutic aspects and we have noticed that our cases, as well as those of the other authors published up to then under the name of congenital, idiopathic and familial methaemoglobinaemia, must be placed into the group of "H.M.C." disease,

to the nosologic entity of which we had already drawn the attention of the medical world.

Our personal cases constitute, undoubtedly, an example of hereditary transmission of the morbid trait, according to the dominant character and to the principles of Mendel. According to *Lamy* and his associates, there are many difficulties in any study concerning hereditary disease. We know very well the difficulties which the genetologists face in investigating the human diseases from a genetic point of view.

The limited human fertility and the prolonged life span of men, hinder the observation on a great number of people and generations. There is also the difficulty of ascertaining the real relation and the impossibility of experimenting on human beings. Whenever the genetic study deals with rare diseases, as the haematologic are, the obstacles are even greater. One of the methods which, quite correctly, is widely used, is the comparison of the monozygote twins. But whenever we face a rare disease among a community, the chances of encountering this disease in a monozygote couple is very remote. In fact, for many of these diseases we have no observations on twins.

The genealogic and statistic studies need a delicate interpretation. In predominant diseases a detailed analysis of some generations, well selected, allows one to obtain quickly reasonable proof. On the other hand, the proof of the recessive character in a hereditary disease which is rare, requires the statistic study of a great number of additional instances and often the use of very difficult mathematics.

Although we possess information concerning many affections, there are others in which the influence of the heredity cannot be exactly determined. That is why the investigation of the genealogic trees will provide us with the final answer of the inheritance and the way of transmission of the morbid trait. This is the reason why we have made the genetic study of the "H.M.C." especially on the investigation of genealogic trees.

As we have mentioned, between 1946 and 1956, in addition to the 25 sporadic instances of constitutional cyanosis (idiop., congen., and familial), eight complete genealogic trees appeared, comprising 81 cyanotic patients by birth, without congenital cardiopathy and clubbing of the fingers, including our own trees of the families of "*Vaftochilaris*" and "*Melaniarides*". These families allowed us to separate and identify from the cyanotic diseases a new nosologic entity of the red corpuscle, which we named "Hereditary Methaemoglobinaemic Cyanosis", although some of the authors, who occupied themselves with the subject after us, proposed that this cyanosis be named "*Codounis Disease*" (*Deiminas, Muratore, etc.*).

According to the well known genetic theory of *Morgan*, the chromosomic mutation follows the genotypic way and the dominant character. In the "Vaftochilaris" family indeed, the immediate successive transmission of the morbid trait from the first generation to the second, and so on, until the fourth, is the most characteristic point and follows Mendel's law (fig. 1).

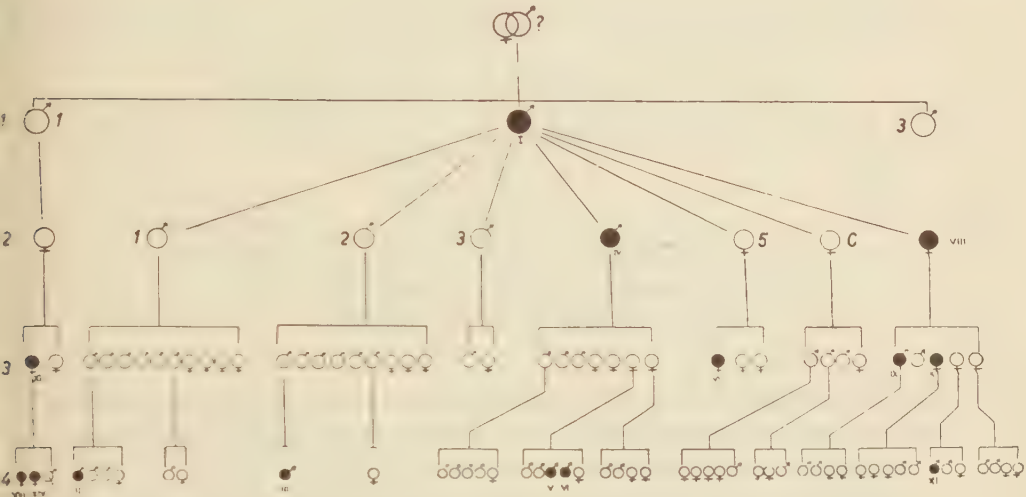


Fig. 1. Genealogical tree of "Vaftochilaris" family.

A. Codounis, G. Loukatos, E. Loutsidis.

In the "Melaniarides" tree (fig. 2) the inheritance at first glance appears to take place through the recessive character. But a more careful study proves that in this tree also the morbid trait is transmitted according to the dominant character. A few empty spaces that one can see in this tree can be easily explained by the fact that the inheritance by one or more dominant genes is slightly penetrating. So the transmission is done by apparently healthy carriers. We should not forget, however, that even in a most favorable environment for the observed dominant trait, one does not always meet with the particularities one expects, because the anomaly is not always present. Some people, carriers of the trait, appear untouched because of incomplete penetration. Sometimes, although the morbid trait is present, it is not recognised because it appears in a minor form which does not permit accurate identification.

On the other hand, one should not forget the multiple difficulties the investigator faces in studying the genetic and the human heredity, nor

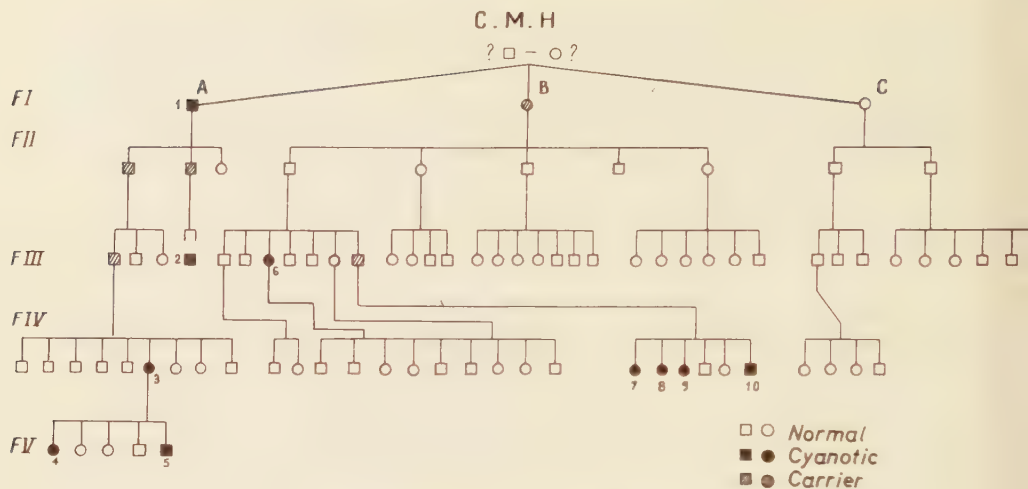


Fig. 2. Genealogical tree of the "Melaniaride's" family.
A. Codounis, G. Loukatos, E. Loutsidis.

should one forget the fact that in the transmission of the trait various factors enter and mechanisms, which sometimes we ignore:—factors due to the genes, the environment, circumstances, etc.

The genetic study of the genealogic trees which appeared after our publications permits no doubt that the transmission of the morbid trait in the "H.M.C." follows exactly the dominant character, as in the "Vaftochilaris" tree. Similarly in the genealogic trees of "Hörlein" and "Weber" (fig. 3), of "Lutembacher" (fig. 4), and "Zacopoulos" (fig. 5 and 6), of

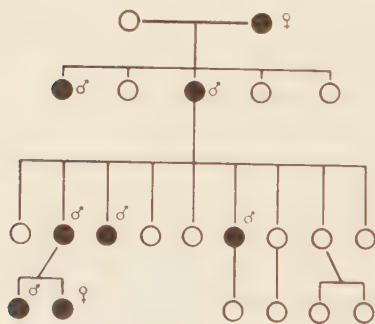


Fig. 3

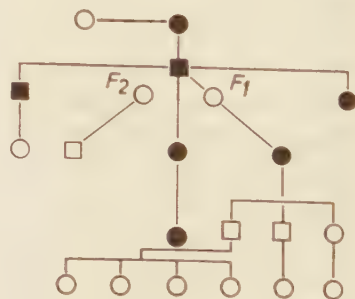


Fig. 4

Fig. 3. Genealogical tree of "Hörlein and Weber".

Fig. 4. Genealogical tree of "Lutembacher".

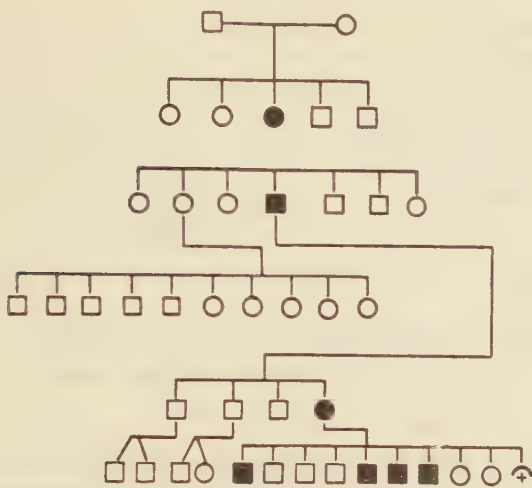


Fig. 5. Genealogical tree of "Tripolis". Zakopoulos.

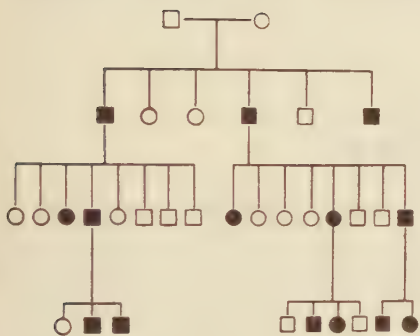


Fig. 6

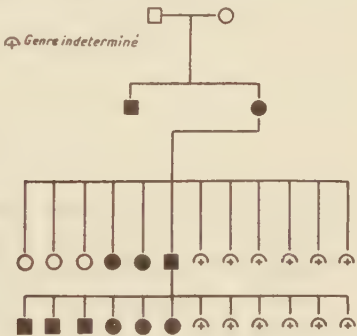


Fig. 7

Fig. 6. Genealogical tree of "Ptolemais". Zakopoulos.

Fig. 7. Genealogical tree of "Balzan and Sugarman".

"Balzan" and "Sugarman" (fig. 7), and of "Recknagel" and "Horlein" (fig. 8), the morbid trait is transmitted, undoubtedly, according to the dominant character. Therefore, the opinion of some writers, such as Gibson and Harrison, Brekey et al., Croizat et al., as well as of others mentioned by Gates, that the heredity of "H.M.C." can be transmitted according to the recessive character, cannot be accepted, especially when their observations concern only one family or some isolated cases of

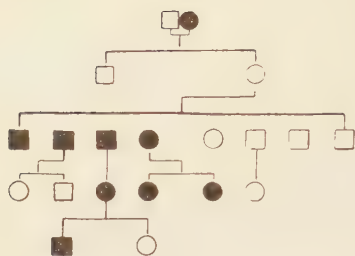


Fig. 8

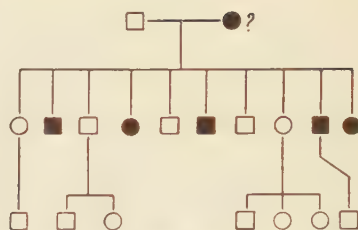


Fig. 9

Fig. 8. Genealogical tree of "Recknagel and Hörlein".

Fig. 9. Family of "Lian, Frumusan and Sassier".

Cyanosis (see fig. 9, 10, 11, 12). Especially in the recessive heredity, as it is known, we must compare and study the genealogic trees and not a few sporadic instances.

Professor Lamy, in his remarkable inaugural lesson, correctly stressed that: "The problem is even more difficult whenever it concerns the recessive



Fig. 10. Family of "Gibson and Harrison".

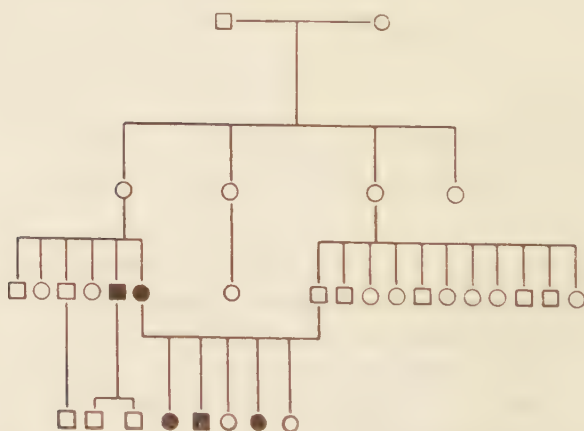


Fig. 11. Family of "P. Croizat, P. Bonnet, J. Favre-Gilly and Poulet".

trait, because here one expects to find one patient against three healthy ones. But the proportion of one against three is not easy to appear, unless a great number is involved. Unfortunately, the human families are few. The average number of collateral, in the countries where trustworthy statistics are published, is less than three. Under such conditions about nine times out of ten a recessive disease will appear as an isolated one. It will be impossible or difficult for one to recognize it and to define in what way it is transmitted."

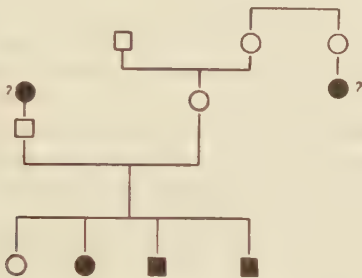


Fig. 12. Family of "C. Worster, Drought, J. C. White, F. Sorgent".

Conclusion

It is our conviction, based on a detailed and assiduous study of eight genealogical trees, that the tare morbid in the "H.M.C." is transmitted by the dominant character. Therefore, the one under the old name, "Congenital and Familial Methaemoglobinaemic Cyanosis" or "Idiopathic Intra-corpuscular Cyanosis", is undoubtedly a hereditary disease transmitted through several generations, both by the males and females. Both sexes can be affected by the disease and transmit it, as it happens with other hematologic disorders, such as congenital hemolytic jaundice (*Lamy*), some cases of thrombocytopenias, spherocytic anaemias, etc.

It appears though that there is a predominance as far as the frequency and the transmission of the disease by the males is concerned.

In our present investigation we did not encounter marriages among families of the same blood.

Finally, although among the 127 instances of "H.M.C.", which have been published to date, 43 of them are of Greek origin, the disease is not particularly a Greek one, but it occurs on all the continents. The study of the disease, however, was made on persons of the white race only.

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HEREDITY OF THE JOINT DISEASES

By R. M. STECHER

Genetics as a possible etiological factor in various types of joint disease is commanding more and more attention. In the time allotted to me today it will be possible only to describe the method of inheritance so far as it is known for several different types of joint disease and to discuss the importance of knowledge in this field. The data upon which these conclusions are based have been presented in previous publications.

Heberden's nodes are enlargements of the finger joints due to osteoarthritis [1]. They commonly affect single joints as a result of injury but we are interested in idiopathic Heberden's nodes arising spontaneously near the time of the menopause. They are definitely hereditary, depending upon a single autosomal factor, sex influenced to be dominant in women and recessive in men. After the age of 70, when penetrance is complete, they are found in 30 per cent of white women in Cleveland. Gene frequency reveals three per cent of the population is homozygous affected, 27 per cent heterozygotes and 70 per cent homozygous normals. Thus it is that 3 per cent of men are phenotypically involved or show the trait and 30 per cent of women, 3 per cent plus 27 per cent are involved. The author firmly believes that this is a specific disease of the fingers, any associated arthritis or rheumatism being incidental and unrelated to it.

Rheumatic fever results from streptococcal throat infections in susceptible people [2]. Under climatic and social conditions such as prevail in crowded quarters in New York, London or Edinburgh, family studies have revealed familial involvement in proportions indicating recessive inheritance. That the disease is limited to susceptible individuals in the population was shown by *Rammelkamp* [3] at the Warren Air Force Base in Wyoming. In epidemics of streptococcal infection running through the barracks and observed carefully with throat cultures, rheumatic fever

occurred in only 3 per cent of men who had had streptococcal sore throat. These findings confirmed previous studies in Copenhagen and North Carolina.

Rheumatoid arthritis [4] was found in relatives of patients five to six times as often as in the general population. It is inherited as a single factor autosomal dominant. Gene frequency analysis showed that 1.2 per cent of the population is susceptible and one half of those or 0.6 per cent are affected.

Ankylosing spondylitis [5] occurs fifteen times as commonly in relatives of affected individuals as it does in the general population. It is inherited as a single factor dominant trait with 70 per cent penetrance in men and 10 per cent in women. The genetic constitution is present in six of 10,000 in the general population.

There is a peculiarity in families in which women have ankylosing spondylitis. In these families there is a stabilization in penetrance which makes it complete in both men and women. This was first noted in five sibships in our series and was also true in ten additional families from the literature in which all sibs were accounted for.

Gout [6] has long been recognized as a genetic disease but inheritance has been irregular so no definite pattern of heredity has been identified. Gout has always been associated with hyperuricemia. When the heredity of hyperuricemia was investigated it was found to be inherited as a single autosomal dominant factor which lacks penetrance in both sexes. Penetrance in males is about 85 per cent and in females 15 per cent.

Gouty arthritis seems to develop in any individual of either sex who has a sufficiently elevated serum urate level for a long enough time. This event is less probable in females owing to a lower normal level of serum urate in women and to a lessened effect of the pathological gene in this sex. Plasma urate levels have been found to be higher in men than in women. This is true for normal people, for gouty patients and for hyperuricemic relatives of gouty patients. Men who inherit hyperuricemia often do not show it until after puberty. Women do not usually show it until after the menopause. There is some correlation between the duration and the magnitude of hyperuricemia and the onset of gout. These factors all help to explain why clinical gout is so much more common in men than in women.

Wolfson [7] has recently advanced a new theory of gout. He believes that the inherited susceptibility to gout depends upon an abnormal male sex hormone from the adrenal which interferes with uric acid excretion by the kidney and thereby produces hyperuricemia. These abnormal male sex

hormones produce effects abnormally marked on uric acid excretion but normal on masculinity. Attacks of clinical gout depend upon a second endocrine disturbance, an inability to produce promptly and in adequate amounts needed 11-oxysteroids during periods of stress. This is due to failure of the pituitary gland to release adequate amounts of ACTH. This explains why ACTH is effective in relieving acute attacks of gouty arthritis.

The problem of heredity in osteoarthritis of the hip is an extremely complicated one [2]. This depends upon the fact that osteoarthritis of this joint may arise from a variety of causes and have varying etiologies. Unfortunately, in the advanced or well developed state of osteoarthritis these preceeding predisposing factors are difficult or impossible to recognize. The causes of osteoarthritis of the hip include previous fracture, traumatic dislocation and aseptic bone necrosis, all due to injury without relation to heredity. Congenital dysplasia of the hip, coxae plana, slipped epiphyses and Legg-Calve-Perthes disease are also followed at times by arthritis. In each of these diseases heredity has been demonstrated or suspected. Several of these conditions may have the same fundamental hereditary defect although they differ in their manifestations as to age of onset, sex distribution and proportion of unilateral and bilateral involvement. Since these conditions are not all apparent at birth, are diagnosed with uncertainty and then only after careful roentgenographic investigation, and since some of them tend to heal spontaneously, family pedigrees show irregular involvement with wide deviation from expected Mendelian proportions. Furthermore, no convincing figures have been presented to show what proportion of patients with these primary genetic characters develop osteoarthritis nor does anyone know what proportion of osteoarthritis of the hip depends upon such genetic characters.

Duvernay [8] and others agree that arthritis develops only in pre-existing deformities of the hip, usually subluxation, coxa plana or coxa vara. That this is not entirely so is shown by my recent observation of a well developed osteoarthritis of one hip in a sixty-year-old woman. She brought with her a roentgenogram of the pelvis taken five years before which showed no sign of disease. There had been no injury, infection or other identifiable cause and there was no involvement of other joints.

The information revealed in these studies already has important practical applications. In ankylosing spondylitis and gout special examinations of relatives of affected people reveal the presence of disease or susceptibility arousing greater alertness and allowing earlier diagnosis and more effective prevention and treatment.

Rheumatic fever can now be prevented by early and adequate antibiotic therapy of all streptococcal infections. It is not necessary to treat all the population, only people who have had the disease or are close relatives of such patients.

In a very extensive and carefully controlled study of rheumatoid arthritis it was found that patients differed very little from the controls regarding various infections, unhygienic conditions and social disasters. When it is understood that only one per cent of the population is susceptible to the disease it is seen that all the world may suffer the heretofore unrecognized specific predisposing cause without developing the disease. The initiating factor may be just as specific, just as innocuous and even less closely related from the point of time to the vague, indefinite, uncertain and unrecognizable onset of rheumatoid arthritis as is a streptococcal throat infection occurring within three weeks of the onset in a susceptible individual for rheumatic fever. When this hypothetical initiating stimulus can affect all of the population and arouse this chronic disease in only one per cent of those affected, it is small wonder that it has not yet been recognized.

It seems probable that early diagnoses and effective therapy of dysplasias of the hip may decrease the incidence of osteoarthritis of this joint.

It is obvious that the diseases we have discussed here differ markedly in their very nature, their ages of onset, their sex distribution, their distribution among the different joints of the body, the speed of development and their pathology. They had best be considered separately and not be grouped together.

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HEREDITARY FACTORS IN SOME RHEUMATIC DISEASES

By T. de BLÉCOURT-MEINDERSMA

There is little to be found in the textbooks and handbooks on rheumatic diseases about hereditary factors in rheumatism. As a rule they are more concerned with mentioning of some sporadic cases and only seldom report on precisely executed examinations of an adequate number of patients and controls, together with their relatives. As our interest in the study of these diseases increased we were struck more and more by the occurrence of rheumatism, of a special form or also of different forms, in one and the same family.

As a result of an investigation into the occurrence in families of ankylosing spondylitis (*Morbus Bechterew*), *J. J. de Blécourt*¹ reported in 1949 "out of 296 patients with ankylosing spondylitis (226 men, 70 women) 96 belonged to 39 families; among the 200 remaining cases there was no relationship. This means that in 19.5 % of this series of patients one or more people with the same disease were found among the patient's family. On two occasions four patients—and again on two occasions five patients—were observed in one family". Since then, *Stecher* among others has issued several publications on the "hereditary factors in arthritis" and pointed out the importance of a thorough and profound examination. Examination of heredity in rheumatism may possibly be of help involving the problem of the etiology of the various rheumatic diseases. We are now carrying out the following investigation to obtain an answer on a sound scientific basis to the question: do hereditary factors play a part in rheumatoid arthritis and ankylosing spondylitis?

¹ *J. J. de Blécourt*: Ned. Tijdschr. Geneesk. 95, 3763, 1949.

Three groups of patients are being dealt with:

- (a) 100 patients suffering from ankylosing spondylitis
- (b) 100 patients suffering from rheumatoid arthritis and
- (c) 100 persons not suffering from any form of rheumatism.

Each of these groups has been equally divided over both sexes, ranges from 25 to 40 years old and has balanced proportion from town and country and from different professions. All the persons concerned live in the province of Groningen, in the north-eastern part of the Netherlands, an agricultural area but also with many small and medium industries, a strongly developed middle class, etc. The nearest relations of these 300 persons are the object of our investigation.

As far as possible all these persons were and are questioned by the investigator and, if necessary, examined by a specialist (X-ray examination included) in an out-patient clinic for rheumatic diseases. The whole investigation remains in the hands of one person who collects the results of special examinations and integrates these with the results of the questionnaires, the home visits, etc. This makes assessment of the results easier and more reliable. Patients are interrogated about and eventually examined for the presence of a number of other diseases, for instance: diabetes, psoriasis, allergic diseases, ulcus ventriculi or duodeni, hypertension, other affections of the locomotor system, etc. In the opinion of some workers, one or more of these diseases are often seen in combination with rheumatism. The number of relatives of each probandus to be examined in accordance with our experimental set-up, amounts to ± 30 , so this means that the data of about 9000 people (in addition to the original 300) has to be registered and these people must, if possible be visited personally and possibly examined. These 9000 persons are spread over the whole of the Netherlands. More than half of the total, however, are found in Groningen or neighbouring provinces. It is impossible to check up on a number of them owing to death or emigration. Inquiries are made, however, about these people from relatives, or the family doctor, and we also gather informations from the emigrants themselves by mail in some occasions.

This investigation was started two and a half years ago. More than 8000 of these 9000 persons have now been registered and about 1500 have undergone medical examination. It is evident to date that about 30% are out of reach, through emigration or death, this means that about 1000 people have still to be visited at home and a number of them examined by a rheumatologist. Now that the registration is nearing completion, it can be expected that this part of the investigation will be finished in the

course of this year. After that, the results will have to be worked out with the help of a statistician and only then our conclusions can be made. The various groups will have to be compared with each other and also with the result of the screening of the population in connection with rheumatic diseases.

Examinations for hereditary factors as well as the screening of the population is made possible by the National Health Research Council T.N.O. which acts in close co-operation with regional services and university-institutes in the fight against rheumatism. There has been gratifying co-operation from the people to be investigated as well as from many physicians, medical and other authorities, registrar offices of the various municipalities, etc.

As far as we know such an investigation of so many persons by one investigator under the continual control of experts in human genetics and rheumatology has to date never been attempted elsewhere. It is impossible to report on the results until the investigation is completed and the results are worked out. We can however, already mention the fact that more rheumatism (in all forms) is found amongst the relatives of the sufferers from rheumatoid arthritis and spondylitis ankylopoetica than amongst those of the group free from rheumatic diseases.

We are in agreement with what was reported by *Stecher* in his article on this subject, issued in *Med. Clin. N. Amer.* in March 1955. Among other things he reports: "Rheumatoid arthritis is found among relatives of affected persons five to six times as often as among people in general." Further he says: "In studying the genetics of joint diseases it is important to consider each syndrome separately. Differences between the several rheumatic diseases are striking." In general we agree with *Stecher* and we have given special consideration to this point.

It is of great importance that hereditary factors should be considered very closely, especially in view of our still inadequate knowledge of the etiology and pathogenesis of rheumatism.

If, as it is often admitted, a relationship exists between the various rheumatic diseases, then it may be expected that this relationship will also find expression in the results of our investigations.

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POLYARTHRITIS IN TWINS

By GERDA THYMAN

Some years ago I commenced investigation of hereditary conditions in connection with rheumatoid arthritis (rh. a.). I began the examination using the proband method. During this work, my interest was awakened in the examination of twins. This had formerly been done by several others, for instance, *Edström*, *Weitz* and *Scherer* and many casuistic cases are formerly reported.

To obtain working material, I put a short notice in the medical periodical, *U. f. L.*, in which I requested colleagues and hospitals to assist me by giving me information concerning twins suffering from rh. a. which came to their knowledge. The Copenhagen daily press copied this notice without my knowledge, and in this way it reached the provinces. This proved to be very favourable, for while the notice in the medical journal brought me into contact with one pair of twins suffering from rh. a., the assistance of the press, on the other hand, revealed 12 pairs of twins, one or both suffering from rh. a. The patients themselves contacted me after reading the notice in the newspapers.

Some time later an extensive investigation of twins was started at the Institute for Human Genetics in Copenhagen with the object of contacting all twins in this country. I was given the names and addresses of twins with symptoms which might lead one to suspect rh. a. In this way I got into contact with 14 pairs in which one of the twins suffering from rh. a.

From the beginning I had one pair, which was discovered by *Snorason* and one pair discovered by myself.

In this way the material has attained the total number of 29 pairs with an exact diagnosis of rh. a. in one or both twins.

In working with rh. a. so many different states and different progresses of the disease are encountered and for this reason I decided very

early to investigate only the cases with clinically certain diagnosis, in my opinion, typical deformity of the joints, in almost all cases typical deformity of the little joints of the fingers. Whenever possible I have talked personally with all the involved twins, also with the healthy co-twins, to be certain. Where personal contact was not possible, in most cases owing to death of the twin but a few refused to co-operate, I have included in the material the cases where the diagnosis and description in the charts were typical. In a few cases the diagnosis has been based on a description of the disease by relatives, when that description was so clear, that no doubt about the diagnosis could exist. Only pairs with twins belonging to the same sex are included, on account of the fact that rh. a. is more frequent in women.

The material as stated consists of 29 pairs of twins, the first section, 15 cases, partially selected, the second section, 14 cases, from an unselected material. Meanwhile, three cases from the selected material appeared also in the unselected, and have to be placed in the unselected material.

The selected series thus comprises 12 pairs, six monozygotic, all females, three showing concordance and three discordance. The other six pairs are dizygotic, five pairs are female, and one pair shows concordance, four discordance, while one pair of male twins shows discordance.

The unselected series consists of 17 pairs, eight monozygotic, six females, two males and nine dizygotic pairs, seven females, two males; all of these cases show discordance.

The material as a whole thus consists of 14 monozygotic pairs with three pairs showing concordance, and 11 pairs showing discordance. 15 dizygotic pairs show one case of concordance and 14 cases of discordance. This difference is not significant.

A few cases will be discussed: One of the concordant monozygotic pairs concerns two young women, 34 years old. The disease began for both of them when they were 18. One of them developed serious rh. a. with characteristic deformities of the joints, while the other only had affection of the left wrist and one of the little finger joints. In this case the SAT test was definitely increased. This case was treated very successfully with gold therapy, and now the only findings are slight stiffness and swelling of the left wrist and subjective sensations in the joints. Her sister experiences similar sensations before every menstruation period.

Another monozygotic pair are women, now 69 years old. Both developed typical rh. a. in their 28th year. Now both of them have severely involved joints, typically deformed in a very similar way. A third concordant, monozygotic pair both died many years ago, and the diagnosis

is based on a very typical and accurate description from one of their brothers. The disease began for both of them when they were 18–20 years old, and continued to total incapacity for both, one at the age of 49 years, the other at the age of 56 years. The one dizygotic pair, showing concordance: women, one died at the age of 40 years, while the other survives, now 49 years old. From the age of 35 they both developed rather slight but typical affection of the finger joints.

Further, it is necessary to mention one of the monozygotic pairs, showing discordance. One of the twins has typical, slight affection, which has been present for 25 years. During the past few years, her sister has had pains in different joints. She was treated with ACTH with good effect. She has had no characteristic deformities. When I saw her, there were no symptoms of rh. a. Owing to the age of the twins, now 67 years osteoarthritis is more probable than rheumatoid arthritis.

Finally I should mention three cases, two monozygotic and one dizygotic not included in the material, because it has been impossible to date to obtain an exact diagnosis, and it will probably never be possible. There is little chance of these cases being concordant, but as stated, the information to date have been too vague for an exact diagnosis.

I believe the future will reveal more cases when the extensive investigation of twins proceeds, and perhaps some of the discordant pairs will later develop rh. a. in the healthy twin also. I consider it wiser, therefore, to delay conclusions until all cases in the country are examined.

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THE GENETIC BEHAVIOUR OF HERITABLE DISORDERS OF CONNECTIVE TISSUE

By V. A. McKUSICK

On preliminary survey five disorders seemed to fulfil the following criteria: (1) Heritable nature, (2) primary defect limited to connective tissue, (3) one element of connective tissue primarily involved, (4) that element of connective tissue fundamentally defective wherever it occurs

in the organism. These five disorders are the Marfan syndrome (M), the Ehlers-Danlos syndrome (E-D), osteogenesis imperfecta (OI), pseudo-xanthoma elasticum (PXE), and the Hurler syndrome (H). Some gauge of the relative frequency with which these disorders are identified is provided by the total number of kindreds which were available to study. Tapping all possible sources the numbers were, in descending order, OI, 81 kindreds; M, 59 kindreds; H, 16 kindreds; PXE, 15 kindreds; E-D, 8 kindreds. E-D may be much more frequent than indicated by this enumeration. Mild degrees of hyperelasticity of skin and joints shade imperceptibly into the normal variations for these characters.

There are reasons from other sources for believing that most, perhaps all, hereditary syndromes of man are the result of a single mutant gene. Perhaps the most convincing argument for the single gene hypothesis in the case of these syndromes is that available when it is possible to relate all manifestations of a given syndrome to a defect in a single element of connective tissue. In none of these five syndromes has the basic defect been identified with complete certainty. However, important steps have been made in this direction. It is possible with reasonable certainty to relate all the manifestations to a single defect in each case and construct a "pedigree of causes" for each disorder.

In the Marfan syndrome the elastic fiber is under suspicion because the histologic change in the aorta appears to be primarily an abiotrophic deterioration of that element. What the suspensory ligament of the lens has in common with the aortic media is unclear; if the common denominator were known, the nature of this syndrome might be clearer. The hypermobility of joints, hernia, kyphoscoliosis and flat feet (the ligaments of the spine and feet have prominent elastic fiber elements) are consistent with the elastic fiber theory of the basic defect. How can one account for the dolichostenomelia (long, thin extremities)? One has the impression that there is an unreining of longitudinal growth of the round bones. Whether a connective tissue defect in the periosteum, which ordinarily exercises some control over longitudinal growth, is responsible is speculation.

In the Ehlers-Danlos syndrome recent evidence (*Jansen* [1955] and others) supports the view that the basic defect concerns the organization of collagen bundles into a meshwork. Because of the defective collagen meshwork the skin and joints are free to be moved through an unusually wide range and the skin and blood vessels are abnormally fragile. The normal elastic tissue probably functions in restoring the displaced structures to their normal position. The elastic fibers are more abundant than

normal in some instances, due possibly to the stimulus of repeated unusual stretching.

In osteogenesis imperfecta collagen is defective in the matrix of bone, skin, fascia, ligaments, tendons, joint capsules and sclera leading to the classical manifestations of this syndrome. Histopathologic studies (*Follis* [1952-1953] and others) suggest that the difficulty is in the maturation of collagen beyond the reticulin fiber stage. Whether one holds to the view that the reticulin fiber is immature collagen or not, the histologic findings are those of fibers with the tinctorial characteristics of reticulin where collagen should be. It is highly likely that the basic defect of OI will be defined in fairly precise chemical terms in the next few years.

Pseudoxanthoma elasticum is an abiotrophy probably of collagen, not elastic fiber as previously thought. The dystrophic collagen fibers acquire some of the tinctorial characteristics of elastic fibers—so-called “elastotic degeneration” of collagen. This occurs in the corium of the skin in areas of maximal wear-and-tear of flexural type: in Brück’s membrane of the eye leading to angioid streaks on fundoscopic examination; and in the media of the intermediate and smaller arteries leading to premature calcification, various symptoms and signs of ischemia, and most dramatically repeated massive hemorrhage especially from the gastrointestinal tract.

In the Hurler syndrome an abnormality of polysaccharide, probably mucopolysaccharide, appears to be responsible for the skeletal deformity, cloudy cornea, deformity of the cardiac valves, deposits in the liver, spleen and other viscera. The conspicuous cerebral aspect is less easily accorded with a generalized defect of mucopolysaccharide metabolism.

The pedigree data from this study are consistent with the following modes of inheritance: M, autosomal dominant; E-D, autosomal dominant, frequently with incomplete penetrance; OI, autosomal dominant, again with wide expressivity and frequently incomplete penetrance; PXE, autosomal recessive.

Two genetic varieties of the Hurler syndrome were encountered. A variety, inherited as an autosomal recessive, is the more frequent of the two and more nearly follows the text-book description of the disease. A second variety, inherited as a sex-linked (X-linked) recessive, displayed the following phenotype differences: less regular clouding of the cornea; retardation of intellect less severe; gibbus less frequently present; survival to an older age. Admittedly these phenotypic differences are largely quantitative ones. Were it not for the differences in mode of inheritance, it would be equally valid to explain the two varieties on the basis of a variable expressivity.

The experience of this study is consistent with the view that OI congenita, OI tarda, hereditary fragilitis ossium or osteopsathyrosis with and without blue sclerae are fundamentally one and the same disease with a wide range of expressivity. Specifically the evidence for identity of congenital and late forms of OI are (1) their indivisible clinical intergrading, (2) the qualitative identity of the histologic changes, (3) the occurrence of examples of each in the same family. The existence of a recessively inherited form of the disease cannot be excluded completely.

Contrary to the finding of *Seedorff* [1949], the sex-ratio of the cases of congenital OI was unity in this study. Defining congenital OI as present in any case with skeletal manifestations at birth, the study revealed a total of 16 cases.

Expressivity showed wide variability from family to family. To some extent individual components of a given syndrome displayed independence of behavior as far as expressivity is concerned. For example, in the Marfan syndrome, affected persons in some families escaped grave ocular involvement whereas skeletal and aortic manifestations were present in advanced form.

The interrelationship of expressivity and penetrance and the arbitrary nature of the concept of penetrance as applied to these syndromes is well illustrated. In each of these disorders the threshold of penetrance is dependent on the ability to diagnose the disorder. When a specific diagnostic test for the presence of the basic defect becomes available, it is likely that penetrance will prove to be complete for these disorders.

Full particulars of this study will be available in a monograph entitled *Heritable Disorders of Connective Tissue* (C. V. Mosby Co., St. Louis, 1956).

Discussion

F. C. Fraser (Montreal): I would like to ask Dr. *McKusick* two questions: (1) When does he call a Marfan a Marfan? I see many patients in whom there are suggestive skeletal or other features but often find it difficult to know where to draw the line diagnostically. (2) Given a patient with the Marfan syndrome what is the risk of incapacitating or fatal cardiovascular and ocular complications? Even though the risk of affected children from an affected parent may be 50%, what is the risk of a given affected child having complications? Obviously it is genetic counseling I have in mind in connection with this question.

V. A. McKusick (Baltimore, Maryland): I am frequently asked to see patients who have some lesion such as unexplained aortic regurgitation and who have a somewhat gracile habitus. In these and similar patients it is our practice (1) to do a detailed family survey for more definite cases of the Marfan syndrome and (2) to have an ophthalmologist perform a slit-lamp examination of the suspensory ligament after maximal dilatation of

the pupils. If both of these investigations are negative one simply cannot state whether the Marfan syndrome is or is not present.

There is a second category of patients who may be confusing. These are mentally retarded infants or children who may have arachnodactyly and hypotonia. Ocular and cardiac abnormalities, superficially resembling those of the Marfan syndrome, may be present also. In these cases one has another tool for ruling out the Marfan syndrome: scrutiny of the precise type of ocular and cardiac abnormality present. If this proves to be interventricular septal defect or simple cataract or other lesion which has not been identified in indubitable cases of the Marfan syndrome, one can conclude that this syndrome is not present. The type of case mentioned appears to be the result of intrauterine insult of some sort and is a rough phenocopy of the Marfan syndrome. Mental retardation is not, in my opinion, a bona fide component of the Marfan syndrome.

I haven't any particular information on "risks" beyond the general observation that risk varies from family to family because of varying gravity of disease. In general the past behavior of the disease in a given family is a guide to prognostication. However, each union of an affected person with an unaffected may result in the introduction of the mutant gene into a new genetic environment with change in the pattern of the disease from generation to generation.

G. W. F. Edgar (Utrecht): How can one reconcile the well-established fact that the material deposited in the brain is lipid in nature with the view that the Hurler syndrome is an hereditary disorder of connective tissue, specifically mucopolysaccharide?

V. A. McKusick (Baltimore): This is indeed disturbing to the view that this is an hereditary disorder of connective tissue or at least a disorder in which the primary defect is limited to connective tissue. Is it possible that the primary defect resides in mucopolysaccharide but lipid metabolism, in the brain at least, becomes "gummed up" as it were? I believe you yourself have some ideas which will be presented later in this congress (page 634) and which may help resolve this dilemma.

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HEREDITARY DISEASES OF THE OSTEO-CARTILAGINEOUS SYSTEM COMPARATIVE MORPHOLOGICAL BASIS

By A. GIORDANO

(With Plate V and VI)

I have been interested for many years in the study of hereditary diseases of the skeletal system, with particular reference to those that appear to be spread out to the whole skeleton. Some diseases of this group, such as chondrodystrophy, involve the bones originated by chondrogenesis; others involve the bones derived directly from connective tissue. Further, some pathological conditions are characterized by abnormal formation of bony tissue matrix, such as osteogenesis imperfecta.

An accurate study leads, however, to the demonstration that not only the skeletal system, but also some other tissues of mesenchymal origin, are involved in these diseases.

Morphological research, when performed with the usual histological techniques, may prove inadequate to detect the finest lesions: I applied therefore a series of methods and histochemical reactions that I integrated with biochemical determinations in the belief that the basis of these diseases has to be found in enzymatic disorders.

The anatomical material used in the present research is represented by 6 cases: 4 cases of chondrodystrophy and 2 cases of osteogenesis imperfecta.

My co-worker *L. Pecchiali* devoted particular care to the histochemical research, performed using the following staining methods and reactions:

- *Hematoxylin and eosin* as an orientation method;
- *Masson trichromic method* for fibrillar structures of connective tissues;

- *Yasuma and Ichikawa reaction* (Schiff reagent following oxidation with alloxan) for α -aminoacids;
- *Hotchkiss-hematoxylin reaction* (Schiff reagent following oxidation with periodic acid) and *Gomori reaction* (silver-methenamine-borax solution, following oxidation with periodic acid) for the study of polysaccharides in general;
- *Toluidine blue* (1⁰/₀₀ aqueous solution) for acid mucopolysaccharides in general and for the evaluation of basophilic and metachromatic stain;
- *Ammonia silver nitrate solution* (Fontana) and *silver-methenamine solution* (Gomori) for reducing free radicals.

The biochemical research, by courtesy of Prof. *Zambotti*, Director of the Institute of Biological Chemistry at the University of Pavia, was concerned up to date with the following enzymes: succinic dehydrogenase, cocarboxilase and beta-glycuronidase. These studies were performed on a fragment of costal cartilage, taken for biopsy from a 13 years old subject with osteogenesis imperfecta.

Morphologic Findings

The cases of chondrodystrophy showed the following tinctorial and histochemical behaviour of their various differentiation forms of the cartilage, ranging from very immature forms of chordoid and chondroid type to the more mature form with deposit of calcium salts and an osteoid picture.

Osteoid tissue: the ground substance shows an affinity for *hematoxylin* (partly due to the calcium salts deposit), for *aniline blue* of the Masson method and for *toluidine blue* with an orthochromatic tone. It appears positive to the *Yasuma and Ichikawa*, the *Hotchkiss* and the *Gomori* reactions. It is interesting to point out that the latter method shows a particularly intense positivity of the peripheral part of osteoid lamellae, where cellular elements in osteogenic activity can be seen. This zone, with no calcium salts, is characterized by its affinity for eosin and by being slightly metachromatic toluidine blue (probable deposit of osteomucoid).

Chordoid and chondroid tissues: the ground substance is rather scarce as a whole, and tends to show an affinity for hematoxylin, the more evident the more the cells become vesicular.

The stroma of this tissue, and particularly the capsular portion of vesicular cells, are basophilic and stained with aniline blue and toluidine blue with a definite metachromatic tone. They are also positive to the *Yasuma and Ichikawa* reaction, as well as to the *Hotchkiss* and *Gomori*

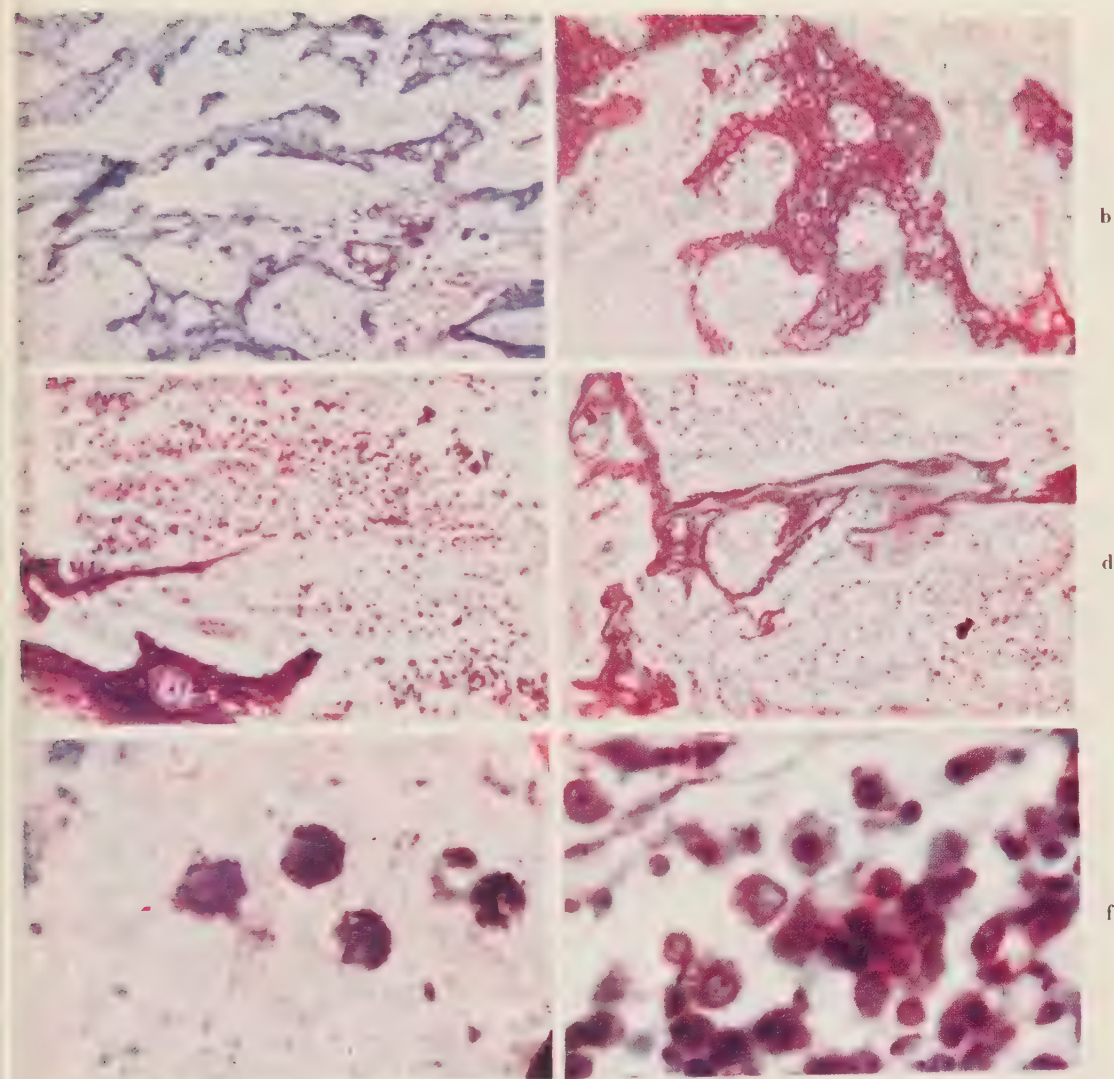


Fig. 2. *Osteogenesis imperfecta*. a) Rib: toluidine blue; b-c-d-f) Femur: Hotchkiss-reaction; e) Rib: Gomori-reaction.

a) Osteocartilaginous lamellae: Vesicular cartilaginous cells intensely metachromatic. b) Osteoid lamellae with vesicular cartilage-like cells. Ground substance intensely positive. c) Osseous lamellae with ground substance intensely positive: Hyperplasia of bone marrow reticular cells. d) Osseous lamellae with varying positivity of ground substance. e) Bone marrow reticular cells with granular cytoplasm. f) Bone marrow reticular cells with intense positivity of intracytoplasmic granules.

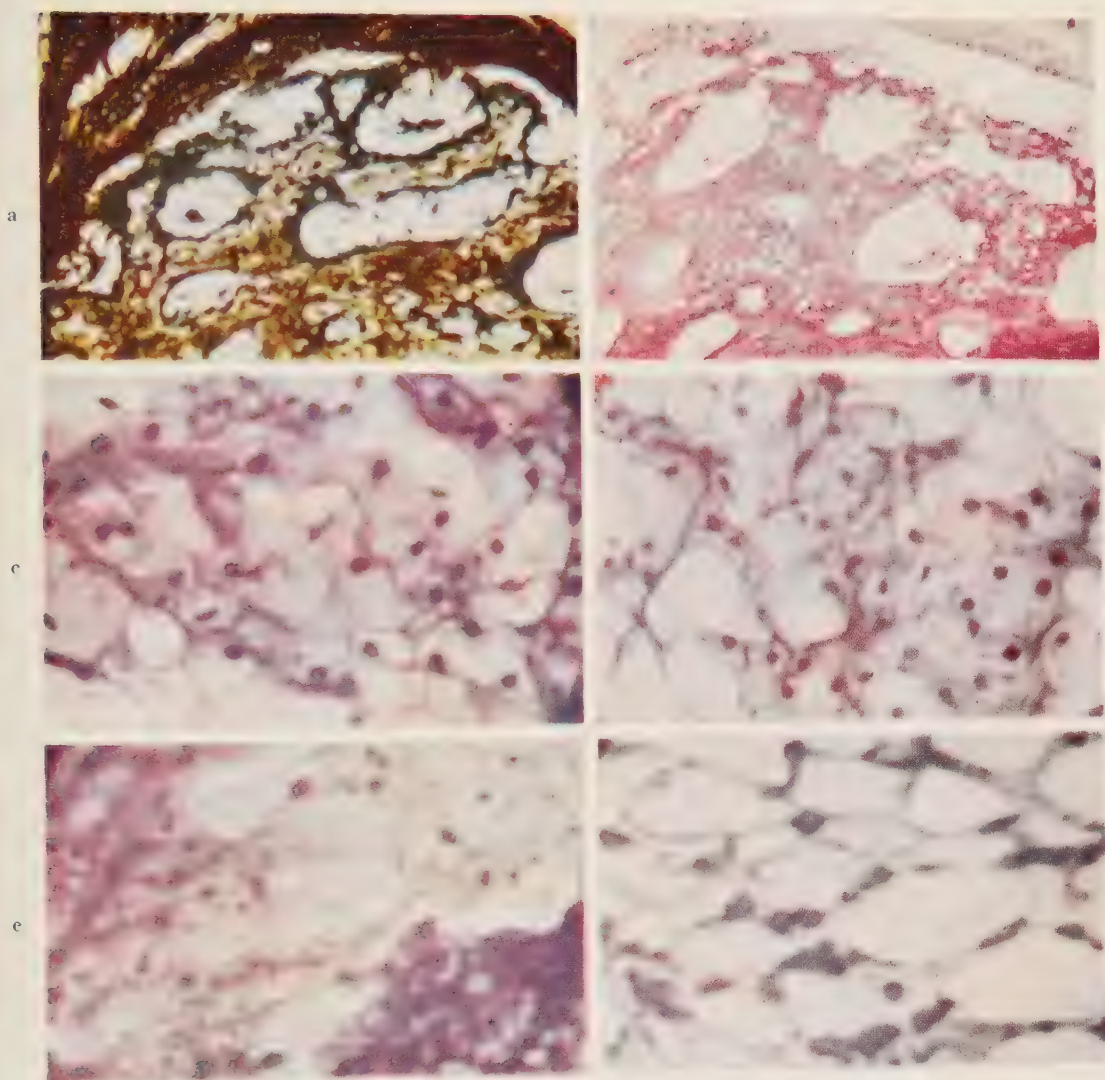


Fig. 1. Chondrodystrophy. Hand: a) Gomori-reaction; b) Hotchkiss-reaction; c-d-e-f) Toluidine blue.

a) Osteoid tissue: Peripheral portion of lamellae intensely positive. b) Osteoid tissue: Ground substance intensely positive. c-d) Chondroid tissue: Metachromatic reaction of vesicular cell capsule and ground substance. e) Subcutaneous tissue: Interstitial storage orthochromatic granular material. f) Subcutaneous fatty tissue: Small masses of homogeneous metachromatic substance, located at the periphery of the cells.

reactions. The latter method can make fibrillar structures evident in poorly differentiated and chordoid-like areas and can also show the amorphous substance, possibly of chondromucoid nature, which forms the capsule of vesicular cells in chondroid tissue.

In addition to these findings in the cartilage, a particular behaviour was found for subcutaneous connective tissue, and more precisely for the amorphous interfibrillar substance and for fat tissue cells.

Fibrils are often dissociated by the accumulation of finely granular amorphous material in lacunar spaces or cavities. This material does not seem to maintain any connection with the cells; it stains orthochromatically with toluidine blue and gives positives Yasuma-Ichikawa, Hotchkiss and Gomori reactions. It would appear therefore to be a glycoproteic material, probably possessing a different chemical nature when compared with normal connective tissue interstitial acid mucopolysaccharides, which are definitely and characteristically metachromatic and usually represent the main portion of the interstitial amorphous substance.

The distinction between these two substances is possible on the slides I observed, since there can be seen both areas with interstitial accumulation of granular orthochromatic material and areas with normal metachromatic interstitial substance.

The other interesting observation can be made on fat tissue. In some instances its cells do not appear completely devoid of their content as it is usual in paraffin embedded specimens. The material, that so proved resistant to various solvents, appears to be made out of small masses of irregular shape, variously located inside the fat cell cavities. These small masses are practically chromophobic with hematoxylin and eosin and Masson, while they appear intensely metachromatically stained with toluidine blue.

The possibility of a lipoid nature of this material was considered: a pyridine treatment made the chromophilic stain with toluidine blue completely fade away.

It is difficult to assess the nature of these lipoids: the negative Hotchkiss and Gomori reactions should exclude the glycolipidic nature at any rate (glycolipids are Hotchkiss-positive because of their glycidic component). On the other hand, this picture was particularly observed in a case in which the specimens had been kept in formalin for a rather long time, and one should consider the possibility of such treatment inducing a polymerization and consequently a gradual insolubilization of neutral fats and fatty acids, which could explain both the resistance to xylene and the metachromatic staining with toluidine blue (due to the polymerization of the acid groups of fatty acids).

To answer these questions, control material of the same age, kept in formalin for the same length of time, was examined. In paraffin-embedded specimens subcutaneous fat appeared to be completely dissolved and staining with methods, particularly with toluidine blue, did not reveal any positive finding.

The hypothesis that in chondrodystrophy the subcutaneous fat has an abnormal composition should be considered valid. The soundness of this hypothesis will naturally become apparent from the study of fresh frozen specimens which will allow a certain definition of such lesions.

In the cases of *osteogenesis imperfecta*, a particular histochemical behaviour may be observed in the ground substance of those osseous and osteoid lamellae that showed already, to the usual histological methods, some morphological changes with a vesicular capsulated appearance of the cells which thus acquire the characters of cartilage cells.

In this case the ground substance appears basophilic, gives a metachromatic stain with toluidine blue and is far more positive to the Hotchkiss and Gomori reactions than it is usual for bone tissue. Such histochemical findings are in all probability due to the presence of a particularly large amount of chondroitinsulphuric acid.

Another interesting observation may be made on the bone marrow: it shows a diffuse hyperplasia of the fixed histiocytic cells, together with an increase of megakaryocytes and binuclear or trinuclear megakaryocytic cells.

Reticulum cells are characterized by a definite positive cytoplasmatic Yosuma-Ichikawa reaction, indicating a high amount of proteins with high α -aminoacids content. A similar intense positivity was seen with Hotchkiss and Gomori reactions which also showed a thick cytoplasmatic infarction of granules to be considered of polysaccharidic nature. These cells cannot be identified with normal haematopoietic elements in their different stages of maturation. It would be justified to consider them as reticular cells in a particular metabolic situation revealed by the presence of cytoplasmatic polysaccharidic granules.

The biochemical research on a fragment of rib cartilage, taken for biopsy from a 13-year-old patient with *osteogenesis imperfecta*, showed the complete absence of succinic dehydrogenase and cocarboxilase; beta-glycuronidase was present with an activity of about 100 U.

It has not yet been possible to carry out any comparative study on normal subjects, because of the obvious difficulty of obtaining biopsy specimens: I am therefore, not in a position to give a comparative value to the present data.

Not having human normal material, I thought it useful to study the enzymatic activity of connecting cartilage and rib cartilage in young rabbits. The results demonstrate that succinic dehydrogenase and cocarboxylase are present in connecting cartilage and, although to a lesser extent, in rib cartilage. As far as beta-glycuronidase is concerned, an activity of 300 U. was found in rib cartilage.

With all the limitations that must be set when comparing the results of human and animal studies, still I think I must point out the total absence of succinic dehydrogenase and cocarboxylase of rib cartilage in the case of osteogenesis imperfecta, as well as the presence of beta-glycuronidase with an activity of about one third as compared with rabbit cartilage.

I consider that the entire morphological and histochemical data I have described may lend well founded support to the concept that both in osteogenesis imperfecta, and in various forms of chondrodystrophy, the mesenchyma is involved in other regions, apart from that involved in osteo- and chondrogenesis.

The observation of a hyperplastic activation of the reticular histiocytic cells of bone marrow in osteogenesis imperfecta suggests a disorder of mesenchymal metabolic activities.

Similarly, the particular histochemical behaviour of the amorphous interstitial substance and of subcutaneous fat tissue in achondrogenesis demonstrates an involvement of this tissue in addition to bone and cartilage.

After the definition of these morphological and histochemical data, particular significance is acquired by the demonstration of a disorder of the enzymatic situation in the cartilage in osteogenesis imperfecta: this disorder is characterized by the complete absence of succinic dehydrogenase and cocarboxylase and by a relatively low beta-glycuronidase content.

I believe I can trace back the morphological and histochemical changes of the bone and cartilage mesenchymal regions with certainty to this enzymatic deficit, and, on the other hand, it seems to me that the importance that these data may have for genetics must not be forgotten, especially if we remember the connections which probably exist between genes and enzymes.

The supposition is to be made that systemic hereditary diseases of bone and cartilage tissues are pathogenetically bound to deficits of enzymatic complexes.

I think that further research should be oriented in this direction.

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HEREDITARY FACTORS IN LONGEVITY

By R. J. van ZONNEVELD and A. POLMAN

It is generally known that hereditary factors have influence on the length of life of the individual. There are many publications with regard to length of life and heredity; *Pearl* especially has occupied himself with this problem.

One of us (*van Zonneveld*) made an inquiry with regard to health problems of old people (Thesis, Groningen 1954). 3000 people of 65 and over have been visited and a great deal of data concerning the circumstances of these people has been collected.

The age of death of 4708 parents of these persons was known. The group was divided according to age in 4 subgroups (65-69 incl., 70-74 incl., 75-79 incl. and 80 and over).

On closer examination of the figures it seemed possible to use them for a statistical evaluation of the relation between hereditary factors and longevity.

We accepted as a criterion for longevity the attainment of the age of 80 and over and put the following hypothesis: If hereditary factors influence longevity, one can expect a difference between the youngest and the eldest group as regards the percentage parents who attained the age of 80 and over.

Comparing the groups we found:

26,3% of the fathers of 315 men of 65-69 reached the age of 80 and over
30,0% of the fathers of 253 men of 80 and over reached the age of 80 and over

X^2 0.945 P 0.50-0.30

34,7% of the mothers of 311 men of 65-69 reached the age of 80 and over

39,5 % of the mothers of 248 men of 80 and over reached the age of 80 and over

X^2 1.363 P 0.30-0.20

30,5 % of the parents of men of 65-69 reached the age of 80 and over
34,7 % of the parents of men of 80 and over reached the age of 80 and over

X^2 2.269 P 0.20-0.10

27,2 % of the fathers of 316 women of 65-69 reached the age of 80 and over
32,5 % of the fathers of 237 women of 80 and over reached the age of 80 and over

X^2 1.812 P 0.20-0.10

32,2 % of the mothers of 326 women of 65-69 reached the age of 80 and over
41,5 % of the mothers of 258 women of 80 and over reached the age of 80 and over

X^2 5.322 P 0.05-0.02 X

29,8 % of the parents of women of 65-69 reached the age of 80 and over
37,8 % of the parents of women of 80 and over reached the age of 80 and over

X^2 6.949 P 0.01-0.001 XX

26,8 % of the fathers of 631 men and women 65-69 reached the age of 80 and over

31,2 % of the fathers of 490 men and women 80 and over reached the age of 80 and over

X^2 2.661 P 0.20-0.10

33,4 % of the mothers of 637 men and women 65-69 reached the age of 80 and over

40,5 % of the mothers of 506 men and women 80 and over reached the age of 80 and over

X^2 6.118 P 0.02-0.01 X

30,1 % of the parents of these men and women 65-69 reached the age of 80 and over

35,9 % of the parents of these men and women 80 and over reached the age of 80 and over

X^2 8.553 P 0.01-0.001 XX

X: significant on the 5 % level, XX on the 1 % level.

Though some of the differences are not significant, others show a distinct significance. From this comparison, we can safely conclude that heredity influences the attainment of old age. Because the people were still alive during the period of investigation, it would only be possible to find the exact figures within 20 or 30 years.

Otherwise, this investigation reveals no new facts; it only underlines known facts.

BIOCHEMICAL GENETICS

Williams, R. J.: Acta genet. 7, 163-175, 1957

The Clayton Foundation for Research, the Biochemical Institute and the Department of Chemistry, The University of Texas, Austin, Texas, U.S.A.

BIOCHEMICAL GENETICS AND ITS HUMAN IMPLICATIONS

By R. J. WILLIAMS

It is both a pleasure and a high honor to be asked to speak to this distinguished Congress. Particularly so because although some of my research has impinged on the field of human genetics, my training has not been in this area. Because of my position as an "outsider" I will bring to you a point of view which may be very different from what it would be if I were thoroughly grounded in the lore and traditions of genetics.

In order for me to develop the thesis which I wish to present, namely that *biochemical genetics has far more importance and far wider implications than is commonly appreciated*, it will be necessary for me to extend my observations beyond biochemistry into the field of human anatomy. Biochemistry is always build upon anatomy. We are rarely interested, for example, in the chemical reactions taking place in *the body as a whole*; we are more often concerned *with* the biochemical transformations which are characteristic of specific organs or tissues.

Let us look first at some of the variations in human anatomy observed among normal individuals, and consider the probability that genetic factors are important for their development. Although the textbook picture of the human stomach is well stereotyped, actually on the basis of a recently published Atlas of Human Anatomy [1] there are enormous variations in shape and about a 5-fold variation in size. The position of the lowest portion of the stomach relative to the sternum, in normal individuals may vary in height through a range of about 20 cm. Livers likewise vary greatly in shape and position and at least 3-fold in size. The length of the small intestine is commonly said to be 22 ft. but even when only a few autopsy specimens were measured recently they were found to vary (in men and women) from 11 ft. to 25 ft. 9 inches [2]. The transverse colon varies in its position in the

visceral cavity in that in some individuals it may be as much as 12 inches lower than in others [1]. The forms of the pelvic colons may be classified into nine different types, and it becomes immediately evident that wide variation in problems of elimination would be expected to result from these anatomical differences alone.

I must not take time to discuss how I believe these differences between normal human individuals are *important* but at this point I wish to emphasize that genetic factors come into play with respect to all of them, and that these are matters that have received very little if any attention from geneticists.

Musculature throughout the body is far from uniform in different individuals. As an instance, there are 11 patterns involving the extensor muscle of the index finger alone! These differences in muscular patterns are present throughout the body and are associated with bone and tendon differences. There are, for example, 8 patterns of the extensor tendons on the back of the hand [1]. These hand differences are no doubt associated with the fact that each individual develops a characteristic signature. Muscular and other differences are also associated with the fact that each individual has a highly characteristic breathing pattern, has distinctive heart action (as shown by blood pressure tracings and electrocardiograms), and exhibits individuality in his manner of performing any gross muscular activity, such as walking, running, throwing, rowing, etc., as well as such delicate operations as those in which, for example, tweezer dexterity is involved.

The blood vessel patterns in the bodies of real individuals do not follow any single textbook picture. The major arteries arising from the aortic arch may be from two to four in number, and when there are four, they are not necessarily the same four indifferent individuals [1]! The size of the carotid artery which carries blood to the brain varies greatly from individual to individual—as do all other vessels which carry blood to specific localities. These variations are superimposed upon those existing in the heart. The pumping capacities of the hearts of young men—even though they are healthy and normal—vary over more than a 3-fold range [3].

Endocrine glands vary widely from individual to individual. Thyroid glands, for example, may vary in weight, among normals, from 8 to 50 grams [4], the parathyroids (two to twelve in number) vary in weight from 50 to 300 mg. The testes in normal males weigh from 10 to 45 grams; the ovaries in females vary in weight from 2 to 10 grams and contain at birth from 30,000 to 400,000 ova. The pineal glands weigh from 50 to 400 mg., and pancreas glands contain from 200,000 to 2,500,000 islets of Langer-

hans [5]. The adrenal cortices of different individuals are said to vary about 10-fold in thickness [6]. It should be emphasized that the values given above are "normal" ones. Other values outside the above ranges are not infrequently encountered, but they are regarded as abnormal.

Our entire nervous system is subject to the same wide variation, which is not only anatomic but physiological as well. The distribution of the numerous different kinds of nerve endings in various locations in the body must be distinctive for each individual; even the patterns of the nerve trunks are distinctive. There are, for example, eight distinct types of patterns of the facial nerve, each possessed by from 5 to 22 per cent of people [1]. The lower point at which the spinal cord terminates in the spinal column in different individuals varies by about three vertebrae; the point of entrance of different nerves varies similarly. Most people have two splanchnic nerves, but some have three. Some do not have direct pyramidal nerve tracts in the spinal cord. In a recent study of recurrent laryngeal nerves in 100 cadavers it was found that of the 200 nerves present, 57 per cent entered the larynx without branching whereas 43 per cent were divided-trunk nerves with from 2 to 6 branches [7]. If we are considered to be "bundles of nerves", each of us is a very different kind of bundle, and the anatomical variations are accompanied by variations in physiological performance.

The variation in anatomy is also very evident in our brains. *Lashley* [8], in an authoritative review, states: "The brain is extremely variable in every character that has been subjected to measurement." At another point, he says: "Even the limited evidence at hand, however, shows that individuals start life with brains differing enormously in structure; unlike in number, size, and arrangement of neurons as well as in grosser features." While there is no need to overemphasize the importance of our brains, anatomically speaking, or oversimplify their functions, it will be generally agreed that they do have something to do with thinking processes. When brains are so very different from one another, we should not be surprised that thinking among human beings is far from uniform.

Two thoughts need to be emphasized with regard to anatomical differences. First since they are morphological in nature it seems certain that genetic factors are involved in their production. Though finding out precisely *how* the inheritance factors operate will doubtlessly prove to be a highly complicated task, the fact that *they operate* can, with considerable safety, be taken for granted. This fact I regard as important, because the anatomical differences are themselves potentially of great importance in human life.

Secondly it can be stated with certainty that there is no human individual who has "about an average" anatomical make up. Suppose we consider for example 10 anatomical items that can be rated quantitatively and which are (for purposes of illustration) independent variables. The chance that any individual picked at random from the population will exhibit a value for one item in the middle 50 per cent of the range will be 1 in 2. However, the probability that he will exhibit values within the middle 50 per cent range for *all 10 items* is only 1 in 1024!

Next let us turn our attention to biochemical differences between normal human beings and point out, in view of the extensive work that has been done in the field of biochemical genetics, that genetic factors are undoubtedly concerned with the production of these differences also. The fact that genetic factors are involved (and probably in a very important way) is worthy of our attention, whether or not we care to work out the details of exactly how each biochemical difference arises. There can be no doubt that our potentiality for producing enzymes arises from inheritance and there would seem to be no reasonable doubt about the widespread occurrence of partial genetic blocks which operate to make the biochemical patterns in each of us highly distinctive.

The evidence for the existence of biochemical differences of great magnitude among the general population is of five different kinds, and in the time allotted it will not be possible to do more than touch briefly upon instances in these different areas*.

1. *Compositional differences.* Relatively a large amount of information is available regarding the composition of blood of individuals because repeated samples can be collected and analyzed. The existence of blood groups has been recognized for over fifty years, and it is now well established that the individuals are distinctive with respect to the content of immune substances in their blood. The protein-bound iodine of the blood varies from individual to individual over at least a 5- to 10-fold range [9, 10, 11], and remains relatively constant for each individual [12]. The bloods of different individuals vary in their content of various types of lipides; and in the case of cholesterol, lipide phosphorus, and titrated fatty acids, at least, the individual differences are persistent [13].

The digestive juices of different individuals vary in composition. The hydrochloric acid content of gastric juice of well adult individuals collected

* Further information on this subject is presented in a forthcoming book, *Biochemical Individuality: The Basis for the Genetotrophic Concept*, soon to be published by John Wiley and Sons, Inc., New York.

under exactly comparable conditions varies from 0.0 to 66.0 meq. per liter [14]. This latter value is twice the mean value. Some normal individuals have at least 400 times as much pepsin in their gastric juice as others [15].

We are different even in our bones, as is shown by a recent study in which it was found that the bones of normal young men of the same age vary in density over 5.7-fold [16]! These densities were determined by careful X-ray measurements of the *os calcis* (heel bone).

2. *Enzymatic differences.* Most of the chemical reactions taking place within our bodies are catalyzed by specific enzymes which are produced in our bodies from the food that we eat. The potentialities for producing these numerous enzymes clearly reside in the genes which we get from our forbears.

Repeated samples of blood from the same individuals have been studied sufficiently so that we know about the content with respect to four enzymes: alkaline phosphatase [17], arginase (corpuscles) [18], choline esterase [19], and amylase [20]. In the case of each of these, every individual tends to maintain a characteristic level, and the variation between individuals is from 3-fold to 50-fold. Other enzyme levels, in general, probably would show distinctiveness also if the necessary data were collected. Two individuals of the same height and weight may have basal metabolisms (summation of the oxygen consumption of every organ and tissue) which are about the same, but the details of the metabolism of each may be very different indeed from those of the other. Some specific chemical reactions may be taking place ten times as fast in one individual as in the other. That this is actually so is shown by an experiment in which the utilization of the amino acid D phenyl alanine was repeatedly measured in the same individuals [21]. Of the four individuals tested, one utilized it to the extent of 94 per cent, one 61 per cent, one 31 per cent, and one 3 per cent. Even in this very small group there was a 30-fold spread with respect to the one item.

3. *Excretion patterns.* Extended investigations in our laboratories, involving the use of some of the newer tools of analysis, have shown conclusively that each individual exhibits a distinctive urinary excretion pattern [22]. This can best be shown in charts in which are depicted, through use of polar co-ordinates, not only items present in the urine (Nos. 18 to 31), but also taste sensitivities for common substances (Nos. 1 to 5) and salivary constituents (Nos. 6 to 17). Each figure represents the results of a series of studies on one individual, in which the length of each line represents the magnitude of one specific item. Figure 1 represents a purely hypothetical individual who would be exactly average with respect to every item. The

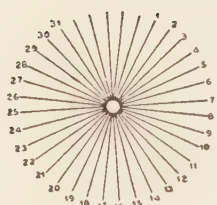


Figure 1

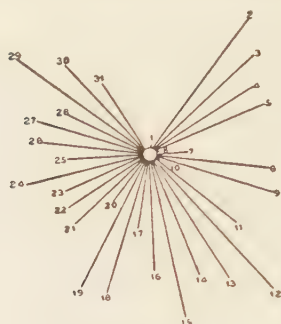


Figure 2

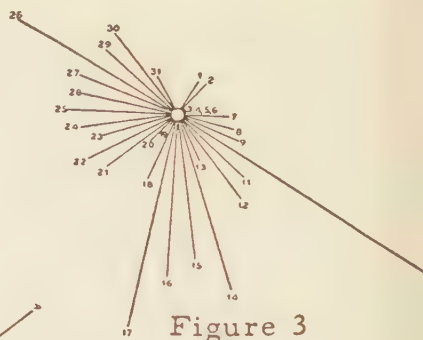


Figure 3

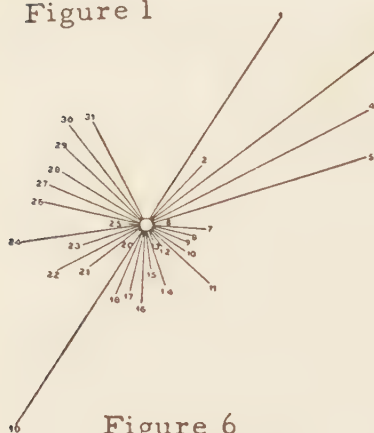


Figure 6



Figure 7

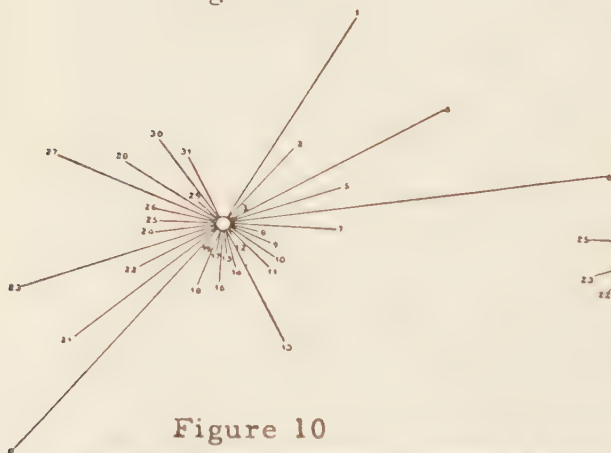


Figure 10

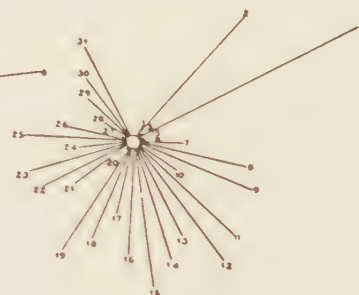


Figure 11

Figs. 1-13. Taste Sensitivity: 1. Creatine, 2. Sucrose, 3. KCl, 4. NaCl, 5. HCl. Salivary Constituents: 6. Uric acid, 7. Glucose, 8. Leucine, 9. Valine, 10. Citrulline, 11. Alanine, 12. Lysine, 13. Taurine, 14. Glycine, 15. Serine, 16. Glutamic acid, 17. Aspartic acid.



Figure 4

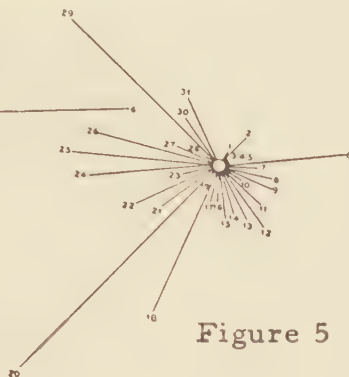


Figure 5

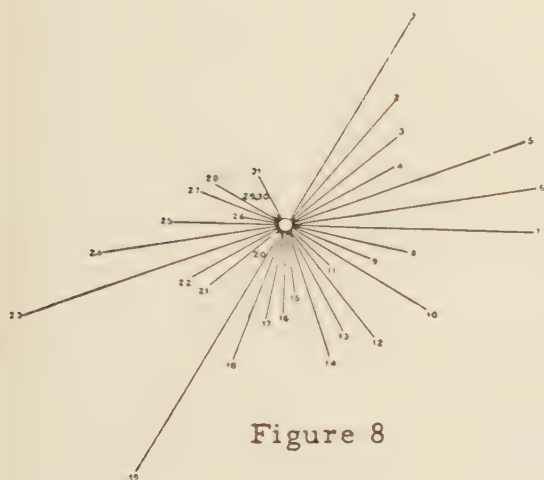


Figure 8

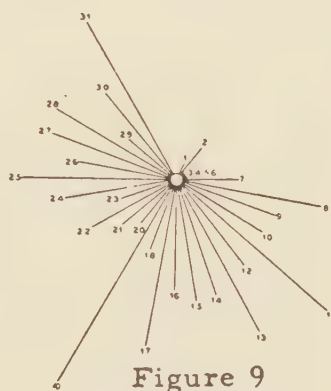


Figure 9



Figure 12

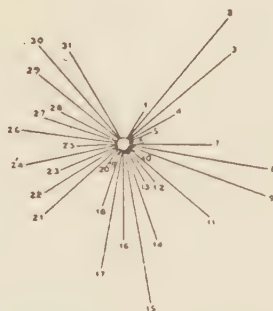


Figure 13

Figs. 1-13 (contd.). Urinary Constituents: 18. Citrate, 19. Base Rf.28, 20. Acid Rf.32, 21. Gonadotropin, 22. pH, 23. Pigment/creatinine, 24. Chloride/creatinine, 25. Hippuric acid/creatinine, 26. Creatinine, 27. Taurine, 28. Glycine, 29. Serine, 30. Citrulline, 31. Alanine.

results for each individual are plotted, using precisely the same scale as was used in the hypothetical case. It is clear that no real individual remotely resembles this hypothetical case. From the standpoint of genetics the close resemblance between figure 12 and 13 should be noted. These are the patterns of a pair of identical twins included in our study.

4. *Nutritional differences.* Two clear-cut cases may be cited in which it has been shown that there is a wide spread in individual nutritional needs for specific substances. A careful study was made of 19 healthy young men, to determine in each how much calcium intake was required in order for the individual to be in calcium equilibrium—that is, free from calcium loss. At one extreme was a young man who needed only 3.52 mg. per kg. of body weight; at the other extreme, the corresponding requirement was for 16.16 mg. [23]. This 4.5-fold range was observed when a small group of 19 young men were studied; if a large group of men and women were to be investigated in this regard, the range would probably be much larger.

Another clear-cut case is that of the amino acid threonine. *Rose* found for a small group of healthy young men that the range of needs was from 0.3 to 0.5 g. per day [24]. For a small group of women the corresponding needs were found to be from 0.1 to 0.3 g. [25]. For men and women taken together, the range is 5-fold, and if the groups of individuals had been larger, the range would doubtless have been larger.

Numerous other nutritional needs would doubtless be found to vary greatly from individual to individual, if the necessary data were collected.

5. *Differences in physiological and pharmacological reactions to chemicals and drugs.* Whenever a chemical or a drug has a physiological or pharmacological effect on an individual, it does so because of an *interaction* between the chemical or drug and some body constituents of the individual. If the *same* drug or chemical affects two people differently, it must be because the body chemistry of the two individuals is not the same.

Among the responses to chemicals which show wide diversity are the taste responses. These involve the specific nerve endings present in the taste buds; and if the taste buds of different individuals were alike in their biochemical functioning, the responses to every chemical would be identical for different individuals.

The majority of people experience an extremely bitter sensation when phenylthiocarbamide is applied to the tongue. To a minority (from about 0 to about 40 per cent depending on the ethnic group) [26] it is completely tasteless.

Creatine, a prominent organic muscle constituent, is bitter to some,

tasteless to others [27]. Sodium benzoate to some is tasteless; to others it is bitter; to other sour; to others sweet; and to others salty [28]. Some individuals find saccharin to have 2000 times the sweetening effect of sugar; to others, it is only 32 times as effective as a sweetening agent [29]. For some, quinine is 256 times as bitter as cascara; for others, it is only twice as bitter. To 15 per cent of people mannose elicited no taste response, to 20 per cent it was sweet only, to 10 per cent it was bitter only, and to the rest it was sweet and bitter in succession.

Richter [30] has found children who could not detect the sweetness of a 20 per cent sugar solution. He also found in a study involving 72 small children, 4 to 10 years of age, that they vary greatly in their liking for alcohol of different concentration. Most of them did not "like the taste" of any concentration above 10 or 15 per cent, but six "liked" samples containing up to 50 per cent alcohol.

In our laboratories we have found that the taste thresholds for such common substances as sodium or potassium chloride often vary, from individual to individual, over at least a 100-fold range [22]. Since all of these observations involve interactions between specific substances and the taste buds of different individuals, they demonstrate the existence of marked biochemical individuality.

Similar evidence is available with respect to the sense of smell. A potassium cyanide solution has for some a strong odor; for others a weak odor; for still others it has no odor whatever. In an experiment involving 244 people, 24 males out of 132 could not smell such a solution at all; only 5 females out of 112 lacked this ability. Further experiments indicate that the inability to smell potassium cyanide solution is a sex-linked recessive [31].

Not only are different responses obtained in experiments involving the special senses, but they may be observed in other cases as well. The minimal concentrations of mercuric chloride required to cause skin irritation in a series of individuals were determined [32]. One responded to a concentration of 1 part per 100,000, another to 3 parts per 100,000, 5 more to 10 parts, 11 more to 30 parts, 13 more to 100 parts, and 4 failed to respond even at this level. This more than 100-fold variation in a relatively small group of 35 is indicative of large differences in microscopic anatomy and body chemistry.

A recent study was made on 29 healthy young men involving the effects of morphine injection [33]. Saline controls were used. The drug caused nausea in 18, sleep in 16, drunkenness in 9, dizziness in 13, itching in 9, and

indistinct speech in 7. It is well known that this drug excites an occasional individual instead of causing depression and that some individuals, unlike others, are prone to become addicts.

Finally, let us consider the physiological effects of alcohol. *Nagle* [34] found that 0.25 ounce of alcohol had the same effect on certain individuals as did 10 times the amount on others. *Jetter* [35] found in a study of 1000 individuals using objective tests, that 10.5 per cent were intoxicated when the alcohol blood level was 0.05 per cent, whereas 6.7 per cent were *sober* when the alcohol blood level was eight times this high—0.4 per cent. Later, a study of 800 more individuals was completed, confirming the earlier observations.

It should be evident that there is a vast array of biochemical items in addition to anatomical ones open to investigation by human geneticists, and that most of these items have not been subjected to genetic study.

An older view of human genetics is embodied in a quotation from an American physician and literary figure Oliver Wendell Holmes "We are all omnibuses in which our ancestors ride, and every now and then one of them sticks his head out and embarrasses us". Too often, I feel, the idea has been prevalent that unless one has one of the clearly heritable diseases, his ancestors are of no consequence in his life. If my view is correct our inheritance shows itself every time we eat or digest or assimilate a meal, every time we sign our name or walk or talk, every time we exhibit our distinctive intellectual or aesthetic powers.

This does not by any means signify that I am a fatalist. Space will not permit an adequate discussion of this subject here. One can still be the driver of his own distinctive omnibus, and can have many roads open, even though some may be closed. The individual who has none of the potentialities of an opera singer cannot choose this road but there are many other roads. One who has such potentialities is not obliged to follow a specific road; he too has numerous options. One who is a fatalist can also be an extreme environmentalist; there is no reason why belief in the importance of heredity should be stigmatized as fatalistic any more than belief in the importance of environment.

Geneticists are well aware of the interplay in biology between hereditary and environmental factors. In the field of social sciences, this is not adequately recognized and little consideration, if any, is given to genetic differences as they relate to human problems. *Toynbee*, for example, appears to discount biological differences as being of any importance in history. He evidently has adopted a current view that genetics is of no importance unless one happens to have a hereditary disease. The only way this com-

pletely erroneous and most unfortunate view can be corrected is for human genetics to investigate "normal" people more intensively.

Scholars in all fields need to divest themselves of both environmentalism and hereditarianism and adopt the *only* view that will stand up biologically, namely that of a genecotarian (gen. ec'.o. tar.ian) who fully recognizes the interplay of genic and ecological factors. This new word is coined because it designates in a sense a new field in which human geneticists must participate. From my point of view it is extremely urgent that we develop expertness in the area which makes possible adjusting the environment, including nutrition, to meet the genetically determined needs of individuals. Up to now expertness in this area is lacking, and no one is qualified to make these adjustments.

Before proceeding further I must say that my interest in the field of genetics does not stem from any exaggerated hopes with respect to the practice of eugenics. Our gene assortments are so complicated and mixed up, that in the great majority of cases decision as to who is "well born" is difficult or impossible. My interest in genetics stems from an interest in the problems of dealing with people as we find them. A little knowledge in this area can be a dangerous thing and can foster racism and all sorts of abuse, but fuller knowledge can only be beneficent, in my opinion.

There are two basic and broadly important reasons why human biochemical genetics has enormous potentialities for the future. One is because it holds the key to the understanding of disease susceptibility. It is my belief that heredity comes into play to a greater or lesser degree not only in the clearly heritable diseases but in *all diseases*; infectious, nutritional, metabolic, degenerative, mental, psychosomatic.

There is one particular possibility which is exceptionally intriguing, namely that many diseases of obscure etiology, may be caused by unusually high nutritional demands (genetically determined) *coupled with* a failure to satisfy these demands [37]. If a developing egg cell gets everything it needs (these needs are distinctive and genetically determined) it will develop normally and be resistant to its enemies. If on the other hand because of partial genetic blocks or their equivalent its demands for one or more of the necessary food elements exceed the supply, it fails to develop in a healthy manner. If the genetic make-up of the developing egg cell is such as to make for augmented demands for certain food elements that are relatively scarce, the resulting individual is liable to be afflicted with genetotrophic disease. We have substantial evidence that alcoholism, for example, is fundamentally a genetotrophic disease [38], and it seems probable that there are *many* others in which genetotrophic factors are prominent.

The other basic reason why human biochemical genetics seems to have tremendous possibilities is because of the contributions it may make to human understanding. The fact that we differ from each other genetically is *politically* a most important one. If we were all built alike we would have the same tastes, in all areas, we could all be regimented and could follow perfectly uniform rules. Our love of freedom is based fundamentally upon our differences in genetic make up. Each of us wants to live his own life and make his own decisions.

Human understanding is bound to lag far behind our understanding of the physical world around us, until human genetics takes its rightful place. The better we understand each other—our differences as well as our likenesses—the better we will get along together. Much of our failure in past centuries is due to lack of understanding and the false assumption that we can “pretend ourselves” into being the same when we are not. Recognition of the differences which actually exist, will greatly increase harmonious human relations.

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Discussion

G. G. Wendt (Marburg): Die von Dr. Williams abgebildeten Variationen in der Form des Magens, der Leber, des Colon und anderer innerer Organe dürften in erster Linie funktionell bedingt sein.

Der typische Gang und die Handschrift eines Menschen hängen primär von den Koordinationszentren im Zentralnervensystem und höchstens sekundär von den normalen Variationen der Muskel- und Sehnenbildung ab.

Die Variation im Gewicht inkretorischer Organe beruht wesentlich auf der gegenseitigen Beeinflussung dieser Organe und auf der hormonellen Gesamtsituation.

Gewiß spielen erbliche Faktoren bei der Ausbildung des gesamten menschlichen Körpers eine Rolle. Es dürfte aber sehr schwierig sein, Erbfaktoren für die normale Variation der Ausbildung innerer Organe zu erfassen. Einmal werden bestimmt sehr viele verschiedene Gene wirksam sein und zum andern wird sich die Bedeutung der Gene nur schwer von nichterblichen Einflüssen (Ernährung, funktioneller Zustand) trennen lassen.

R. J. Williams (Austin, Texas): Questions may be raised with respect to the importance of genetic factors in the production, for example, of stomachs of various sizes and shapes. The importance of genetic factors in the production of different blood vessel patterns and different nerve patterns can hardly be doubted. With respect to the biochemical excretion patterns, for example, we have demonstrated that these are governed in an important way by genetics by studying numerous rats including those of inbred strains. Each animal exhibits a highly distinctive excretion pattern even though the diets are exactly the same. Animals within a closely inbred strain resemble each other markedly in excretion patterns, whereas those of diverse genetic origin exhibit patterns which differ enormously.

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INBORN ERRORS OF LIPID METABOLISM

By G. W. F. EDGAR

Lipidoses are inborn metabolic errors, leading to the accumulation of various lipids in the nervous system and in the reticulo-endothelial system. Judging from their conventional names (table 1) it might be concluded that these lipids are totally different substances. Actually, however, they are closely allied to one another, owing to the fact that each of them, with the exception of cholesterol, contains sphingosine. Therefore the term "sphingolipids" should be recommended as a common group name by which to designate these substances. In the normal organism, the lipids that accumulate in the lipidoses are essential constituents of the neurons. Moreover,

Table 1. Accumulated lipids in various types of lipidosis. Myelin lipids are printed in italics.

Type	Brain	Visceral organs
Cholesterinosis	<i>cholesterol</i>	<i>cholesterol</i>
Gaucher dis.	<i>cerebrosides</i>	<i>cerebrosides</i>
Niemann-Pick dis.	<i>sphingomyelins</i>	<i>sphingomyelins</i>
	+	
	gangliosides	
Amaurotic idiocy	gangliosides	gangliosides
Gargoylism	gangliosides	muco- polysaccharides
Familial leucodystrophy	hexosamine- containing lipid (gangliosides?)	

* Aided by a grant no. 108 from the American Multiple Sclerosis Society.

cerebrosides and sphingomyelins almost solely occur in that portion of the neuron called the myelin sheath. The above suggests that indirect data on the metabolic disturbances in lipidoses might be obtained by studying neuronal lipids and their metabolism in normal nervous tissue.

Observations on the pathochemistry of lipidoses may contribute valuable suggestions on the aspects to be studied. In this respect, attention is called to the biochemical relationship between sphingomyelins and gangliosides, as shown by the simultaneous appearance of sphingomyelin accumulation and ganglioside accumulation in Niemann-Pick's disease in the same family.

Discussion

B. M. Aschner (New York): Asks whether the occurrence of different types of lipidoses in various members of the same family has been observed. This would be interesting in view of the close chemical relationship of the various lipids concerned.

Bearn, A. G.: Acta genet. 7, 177-178, 1957

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WILSON'S DISEASE: IS THE PRIMARY INHERITED DEFECT ONE OF COPPER OR AMINO ACID METABOLISM?

By A. G. BEARN

The collection of 21 patients with Wilson's disease has enabled a detailed study of the biochemical and genetic features of this disease to be undertaken. The relationship between the disturbances of copper and amino acid metabolism have been studied in asymptomatic siblings and in patients at various stages of the disease in an attempt to decide which is the primary inherited defect. Radioactive studies using Cu^{64} have indicated that defective synthesis of ceruloplasmin is responsible for the decreased serum ceruloplasmin found in patients with this disease. Quantitative studies on

the urinary excretion of amino acids have demonstrated that a normal excretion of urinary amino acids may occur in Wilson's disease despite a diminished serum ceruloplasmin. With progression of the disease phosphaturia, glycosuria, uricosuria and albuminuria, in addition to aminoaciduria, develop and become progressively severe. Genetic analysis has shown that the disease is inherited in an autosomal recessive manner in which defective synthesis of ceruloplasmin is probably the primary inherited metabolic defect. Detection of the heterozygote has not yet proved possible. Increased aminoaciduria is a secondary effect due to deposition of excessive copper in the proximal renal tubules.

Milch, R. A. und H. Milch: Acta genet. 7, 178-184, 1957

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DOMINANT INHERITANCE OF ALCAPTONURIA

By R. A. MILCH and H. MILCH

Alcaptonuria is an "inborn error of metabolism" [1] characterized biochemically by an inability of the human organism to disrupt the benzene ring of homogentisic (2,5-dihydroxyphenylacetic) acid. Clinically, it is characterized by the excretion of urine which causes the reduction of cupric to cuprous solutions and which, on standing or on becoming alkaline, tends to become chemiluminescent and to assume a dark, mahogany-brown or even black appearance.

The disorder is hereditary and almost constantly present from birth, though occasional cases have been recorded in which homogentisic aciduria was not detected until later in life. During childhood, it is, at most, a matter of social inconvenience, since the oxidation polymers of the organic acid in both urine and sweat tend to mordant, and hence more or less per-

manently discolor diapers and other clothing. With advance in age, however, the metabolic disturbance constitutes the keystone of a pathognomic, temporally sequential triad of disorders: alcaptonuria, ochronosis and arthritis.

So far as we are aware, with the exception of the atypical arthritis associated with gout, alcaptonuria is the only metabolic disorder of endogenous origin which is characteristically and virtually constantly followed by typical degenerative joint disease, so-called "osteo-arthritis". It appears to be the only known hereditary disorder which practically always leads ultimately to arthritis.

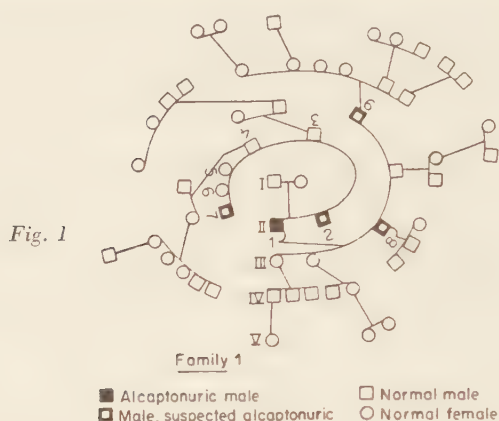
Since *Garrod* first thoroughly investigated the patterns of inheritance in instances of human alcaptonuria, it has generally been maintained that the syndrome is determined by a simple, autosomal recessive gene. Data presented elsewhere [2, 3] and in the current communication are concerned with an alternate genetic hypothesis, which, it is believed, better explains certain apparent incongruities and satisfactorily accounts for the patterns of inheritance previously noted.

Method

Genetic data have been obtained concerning three previously reported kindreds. Knowledge of the state of health, geographic location and other pertinent details concerning the original patients and, where possible, their descendents was obtained from the original reporting physicians, their successors and a variety of governmental and private groups. With but few exceptions, each known descendent was directly contacted. Few, however, could be subjected to physical examination or roentgenographic examination and, with the exception of family 3, there were no attempts to verify previously established diagnoses on the basis of chemical examination of the urine. The urine in each of the individuals in family 3 has been examined for the presence or absence of homogentisic acid in pooled specimens collected over several 24 hour periods. When once established, each pedigree was verified, at about yearly intervals, before it was finally accepted.

Material

Family 1: Attention was originally directed to this kindred by *Marshall* [4], later by *Futcher* [5], and most completely by *Osler* [6]. Despite some ambiguity concerning the identity of the affected individuals, evidence obtained from private records is overwhelming in suggesting that only two, and not three brothers were affected (Fig. 1).



There is no information concerning alcaptonuria in the original parents (I) or their antecedents. Two of the seven children born to them, however, are definitely known to have had alcaptonuria. II-1 is one of these and is the patient seen by *Futcher and Osler*. *Marshall's* patient was either II-2 or II-7. Both have been marked as "suspected alcaptonurics" but since neither has been personally examined nor have had any known descendents, their precise identification is not particularly relevant.

II-3 married a non-alcaptonuric first cousin. II-4 married a non-relative who is known not to have had alcaptonuria. II-5 and II-6 married non-alcaptonuric brothers, but nothing further could be learned about this branch of the family.

It is virtually certain that either III-8 or, less likely, III-9 was the son of *Osler's* patient (II-1). The remaining members of the III, IV and V filial generations are free of alcaptonuria.

Family 2: This pedigree has been presented, in part, by *Pomeranz*, *Friedman and Tunick* [7], *Smith* [8], and *White, Parker and Block* [9]. The family has been completely re-studied and re-evaluated here (Fig. 2). The parents (III) of the probands, IV-1 and IV-2 were first cousins, but not alcaptonuric, and were unaware of any of the components of the alcaptonuric syndrome in any of their forebears. IV-1 married his first cousin and three of his four children, V-6, V-7, and V-8 are alcaptonuric. V-8 has not married. The remaining siblings all married non-relatives who are free of alcaptonuria. VI-9 is clinically alcaptonuric. His parents refuse to permit chemical examination of his urine and, thus, he has been considered here as a suspected and not proven alcaptonuric.

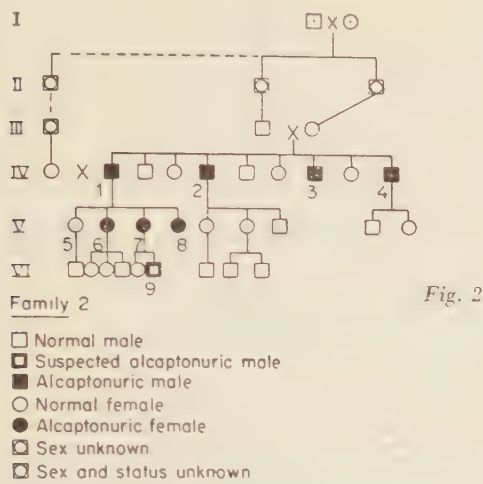


Fig. 2

Family 3: The pattern of inheritance in this family was reported first in 1951 [10] and again in 1955 [3] (Fig. 3). Circumstantial evidence subsequently obtained points strongly to the fact that this family is directly related to that reported by *Pieter* [11]. Unfortunately, certain extra-medical considerations have prevented a complete analysis of the precise relationship. Preliminary data, however, tend to suggest that the original male parent (II-1) of the present pedigree is, in fact, a member either of the third or fourth generations in the pedigree outlined by *Pieter* (Fig. 4). This person is known definitely to have been alcaptonuric and his wife is presumed to have been no-afflicted and non-relative.

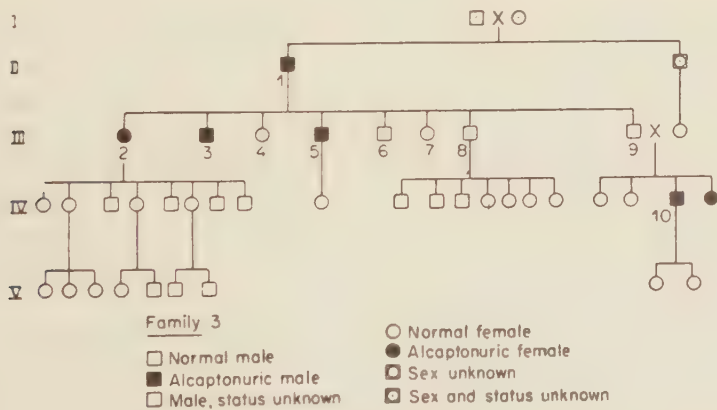


Fig. 3

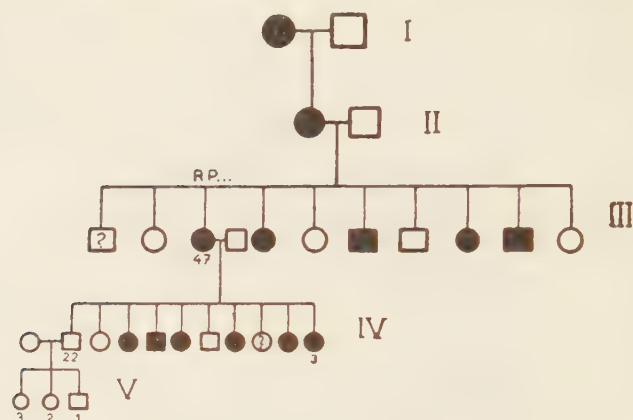


Fig. 4. ○ Male. □ Female. ■ ● Affected. □ ○ Unaffected. ? indicate still-birth.
R. P. = Proband. The figures give the age.

With the exception of III-3, III-4 and III-7, about whom no additional information could be obtained, all of the remaining members of the family have been examined. III-6 is known to have died in neo-natal life. No specific information is available concerning his status as regards homogen-tisic aciduria, although he is believed to have been non-alcaptonuric. III-2, III-5 and III-8 married non-relatives and all of their descendents are free of alcaptonuria. III-9 married his first cousin and his two younger children are alcaptonuric. IV-10 married a non-relative and neither of his two children is alcaptonuric.

Discussion

Physiologically, the components of the alcaptonuric syndrome are manifestations of an inherited absence of failure of at least one enzyme system [12, 13]. The absence of this enzyme system results in an abnormal retention within the body of an otherwise normal intermediary metabolite of the aromatic amino acid phenylalanine and tyrosine (homogentisic acid). Despite the urinary excretion of impressive amounts of this metabolite, profound degenerative changes ultimately arise in the ground substance of mesodermal tissues in consequence of its abnormal retention in this metabolic disturbance.

The genetic basis for the physiological abnormality, however, is not entirely clear. Genetic details are delineated in only a relatively small percentage of the approximately 300 reported cases of the disorder, and even when genetic data are available, they are usually limited to the most

immediate descendents of affected individuals. Little or nothing is usually presented concerning the less lineal relations of affected persons.

The overwhelming majority of the cases reviewed by *Garrod* [1] and *Hogben*, *Worral* and *Zieve* [14] strongly suggest that alcaptonuria is inherited as if in consequence of the action of a single, completely recessive, rare autosomal gene. Despite the effects of consanguinity, it would be highly improbable, under such circumstances, for alcaptonuric individuals to bear similarly affected offspring. There are, however, a number of reported kindreds which present precisely this phenomenon. These include instances recorded by *Orsi* [15], *Fromherz* [16], *Umber* and *Burger* [17], *Toenniessen* [19], *Pieter* [11], *Hall*, *Hawkins* and *Child* [19], *Martin*, *Underdahl*, *Mathieson* and *Pugh* [20], as well as the families reported here.

Pieter's kindred is of especial importance, for there is no question but that it represents an instance of unequivocally dominant transmission. The virtual certainty of the direct relationship of family 3 noted here to that kindred assumes, accordingly, considerable significance. Similarly, the *Hall*, *Hawkins* and *Child* kindred is of particular importance, since, as has been indicated by *Klein* [21] in that large kindred in which there was much evidence of inter-marriage, the data are capable of interpretation in light of an hypothesis of dominance.

In each of the families reported here there has been evidence of direct transmission and, at the same time, of failure of expression within pedigree lines for extended periods of time. This could be interpreted as indicating the possible necessity of more than one pair of co-existent factors for the clinical expression of the disorder.

If it be assumed that the gene for alcaptonuria is an incompletely penetrant dominant, which co-exists with one or more pairs of other gene factors, individuals heterozygous for the gene might frequently fail to demonstrate the effects of the heterozygous state and would, therefore, appear normal. Such an hypothesis would explain the striking excess of consanguineous unions among parents of affected individuals and would adequately account both for the recorded instances of seemingly incongruent dominant transmission and for the more frequently observed apparently recessive mode of inheritance.

Pending a more precise statistical evaluation, which is currently under investigation, the hypothesis is, therefore, tentatively offered that alcaptonuria is an "inborn error of metabolism" which is not genetically determined by a single, autosomal recessive gene, as has previously been postulated, but which may be determined, rather, by an incompletely penetrant dominant gene which co-exists with at least one other pair of modifying gene factors.

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Pfändler, U.: *Acta genet.* 7, 184-187, 1957

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LA MANIFESTATION HÉTÉROZYGOTE ET HOMOZYGOTE DE CERTAINS TROUBLES DU MÉTABOLISME (PORPHYRIE CHRONIQUE, CYSTINOSE, MALADIE DE NIEMANN-PICK)

Par U. PFÄNDLER

Par opposition aux malformations somatiques, les malformations biochimiques héréditaires sont plus fluides, douées de variabilité individuelle, plus ou moins réversibles; elles n'altèrent pas obligatoirement la forme, les dimensions, la structure anatomique des organes. Certains troubles du métabolisme se prêtent tout particulièrement aux études de la phéno-

génèse, et de la manifestation hétérozygote et homozygote du gène pathologique responsable.

Je citerai ici trois exemples tirés de trois domaines différents du métabolisme: la *Porphyrie chronique*, la *Cystinose* et la *maladie de Niemann-Pick*.

1. Un garçon de 8 ans est atteint d'une *coproporphyrurie III chronique* [1], accompagnée d'un retard de croissance, de rachitisme tardif, d'aribo-flavinose et d'hyperaminoacidurie. Il manifeste donc une porphyrie chronique associée au syndrome Debré-de Toni-Fanconi. Ce patient élimine quotidiennement 50 mg. de coproporphyrine III dans l'urine et dans les selles, c'est-à-dire une quantité 50 à 100 fois plus élevée que la norme.

Son père, sa mère, ainsi qu'un oncle maternel et une tante paternelle sont cliniquement sains, mais ils éliminent une quantité de coproporphyrine III qui est 5 à 35 fois plus élevée que la norme. Ce léger trouble du métabolisme des porphyrines se transmet selon le mode irrégulièrement dominant.

Or le parents du proband sont cousins germains. On peut admettre que la forme grave de la coproporphyrurie observée chez ce garçon, n'est rien d'autre que l'expression homozygote du gène qui, à l'état hétérozygote, conditionne chez les parents, chez un oncle et chez une tante, une élimination augmentée de la coproporphyrine sans manifestation clinique.

2. J'ai fait des observations analogues en ce qui concerne la *Cystinose* [2], dans deux souches différentes. La première qui est de Bâle, présente un enfant décédé à un an de cette maladie. Outre la thésaurismose cystinique, le proband manifeste le syndrome Debré-de Toni-Fanconi: retard de croissance, rachitisme, hypophosphatémie, troubles de l'excrétion et de la résorption urinaires (albuminurie, hyperaminoacidurie, glycosurie).

La plupart des éléments de cette souche ont été examinés au point de vue de leur comportement aminoacidurique, en déterminant dans les urines des 24 heures, la quantité absolue et relative d'azote aminé, et en pratiquant la chromatographie sur papier. Or la fréquence de l'hyperaminoacidurie est augmentée d'une manière significative dans la parenté paternelle et maternelle.

Dans la seconde souche que est de la région de Lausanne, un frère et une sœur sont décédés de la cystinose, respectivement à 3 et à 2 ans. Leurs parents ont l'un une hyperaminoacidurie, et l'autre une cystinurie. La fréquence de l'hyperaminoacidurie est aussi augmentée d'une manière significative dans la parenté maternelle et paternelle.

Quelles sont les relations génétiques entre la cystinose et cette hyperaminoacidurie qui se transmet selon le mode dominant? Nous savons que

l'on a enregistré à plusieurs reprises une consanguinité des parents d'enfants cystinotiques. Ici aussi nous pouvons admettre que la cystinose est l'expression homozygote du gène qui, à l'état hétérozygote produit une hyperaminoacidurie sans manifestations cliniques apparentes.

3. Je citerai encore un troisième exemple concernant la *maladie de Niemann-Pick* [3]. Cette dernière apparaît sous 2 types différents: la forme infantile qui est létale, et la forme adulte dont les éléments sont parfaitement viables.

Je présente une famille danoise avec un garçon de 5 ans, atteint de Niemann-Pick. Il manifeste un retard de croissance, une hépato-splénomégalie, et une densification des plages pulmonaires qui prennent un aspect micronodulaire. Les parents du proband sont cousins germains. J'ai déterminé dans le sang de tous les éléments de cette famille, le taux du phosphore inorganique, du cholestérol, et des acides lipiques totaux. Or nous trouvons chez plusieurs éléments une augmentation du phosphore inorganique et des acides lipiques.

J'ai décrit en 1946 les premiers cas de la forme adulte de Nieman-Pick. Ils sont d'origine suisse. Deux frères sont décédés de cette maladie, à 29 ans, et à 33 ½ ans. — Deux autres frères encore vivants, ont l'un une hépato-splénomégalie, et l'autre une hépatomégalie, probablement de la même origine. Chez un grand nombre d'éléments de cette souche, j'ai aussi observé une augmentation significative du phosphore inorganique. D'autre part, la valeur moyenne des acides lipiques totaux est augmentée d'une manière significative par rapport à la valeur moyenne observée dans une population mélangée. La maladie de Niemann-Pick serait donc la manifestation homozygote du gène qui, à l'état hétérozygote, conditionne une légère perturbation du métabolisme phospholipidique, sans manifestations cliniques apparentes.

Les malformations biochimiques héréditaires constituent l'un des domaines qui se prêtent tout particulièrement au dépistage des hétérozygotes.

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Discussion

J. Frézal (Paris): L'hyperaminoacidurie constatée par le Dr Pfändler chez les parents et collatéraux des malades atteints de cystinose concerne-t-elle les mêmes acides aminés ou existe-t-il au contraire chez ces sujets une grande variabilité qualitative dans l'excrétion des amino-acides?

Anderson, E. P., H. M. Kalckar and K. J. Isseibacher: *Acta genet.* 7, 187-188, 1957

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A SPECIFIC ENZYMATIC DEFECT IN CONGENITAL GALACTOSEMIA

By E. P. ANDERSON, H. M. KALCKAR and K. J. ISSELBACHER
(with the technical assistance of B. WAAGE-JENSEN)

Galactosemia constitutes an inborn error of metabolism characterized by an inability to utilize galactose. Normally, galactose is metabolized by first being phosphorylated to galactose-1-phosphate (Gal-1-P) by galactokinase and ATP. Gal-1-P is then converted to glucose-1-phosphate (G-1-P) by two reactions which involve a nucleotide, uridine diphosphate glucose (UDPG) and two specific enzymes:

1. $\text{Gal-1-P} + \text{UDPG} \rightleftharpoons \text{UDPGal} + \text{G-1-P}$ (P-Gal transferase)
2. $\text{UDPGal} \rightleftharpoons \text{UDPG}$ (Galacto-waldenase)

Recently it has been reported by Schwarz et al. (*Biochem. J.* 62, 34, 1956) that erythrocytes of galactosemic subjects, when incubated with galactose *in vitro*, show an accumulation of Gal-1-P, while normal red cells do not. This demonstrates the presence of galactokinase and points to a defect in a subsequent step.

The ability of normal and galactosemic erythrocytes to carry out these other reactions has, therefore, been examined. Hemolysates were incubated with the various substrates and the reactions measured by specific enzymatic

techniques. PGal transferase activity was found to be present in normal cells to the extent of 1 to 2 $\mu\text{M}/\text{ml.}/\text{hr.}$, but there was no detectable activity of this enzyme in the erythrocytes of ten galactosemic subjects. In contrast, galacto-waldenase was present in equivalent amounts in both normal and galactosemic cells. The block in the transferase could not be accounted for by the absence of a necessary cofactor in galactosemic blood; neither was the presence of any inhibitor detected. With a modified enzymatic assay, using radioactive substrate, this defect in PGal transferase could also be demonstrated in liver biopsies from galactosemic patients.

These data strongly suggest that galactosemia represents an example of a metabolic disease, presumably of genetic origin, which is characterized by a congenital defect in a specific enzyme. The metabolic manifestations of the disorder are consistent with this enzymatic defect.

Concerning the question of a "trait", it should be pointed out that at the present time no major difference between non-galactosemic subjects and parents or siblings of galactosemic patients could be detected. However, since the assay is apt to underestimate the values for the first group, an exact kinetic study would be necessary in order to detect any difference between the two groups.

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FAMILIAL LOW PSEUDACHOLINESTERASE LEVELS

By H. LEHMANN and B. RYAN

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HETEROZYGOUS CARRIERS OF PHENYLKETONURIA DETECTED BY PHENYLALANINE TOLERANCE TESTS

By D. YI-YUNG HSIA, K. DRISCOLL, W. TROLL
and W. E. KNOX

The molecule whose dysfunction is responsible for the hereditary disease of phenylketonuria is the liver enzyme concerned with the oxidation of phenylalanine. Inactivity of this enzyme results in the high blood levels of phenylalanine, the excretion of phenylpyruvic acid, and mental deficiency. Genetic studies have established this condition to be completely recessive, and no related mental or biochemical abnormalities have been found in the heterozygous parents or siblings of the patients. *Pauling's* introduction of the term "molecular disease" suggests, however, that the fraction of enzyme stemming from the abnormal gene in the heterozygotes should be defective. This prediction is supported by the present findings from phenylalanine-tolerance tests that known heterozygotes of phenylketonuria have lower capacities for metabolizing phenylalanine than do normal people.

Plasma levels of L-phenylalanine were determined one, two, and four hours after oral doses of 0.1 g. of L-phenylalanine per kg. body weight, given after an overnight fast, in 19 heterozygous individuals (parents of proved phenylketonuric patients) and an equal number of normal adult controls. L-phenylalanine was measured by a modification of the bacterial decarboxylase method of Udenfriend and Cooper. The fasting plasma phenylalanine levels taken before the test in all individuals were within the range of 0.03 to 0.16 $\mu\text{mol/ml}$. The phenylalanine levels in the heterozygotes during the test were on the average about twice that of

the controls at each of the hourly intervals. The distinction between the groups was particularly clear at the fourth hour, and by comparison of the area under the tolerance curve. The test was repeated on several individuals from each group with highly reproducible results.

Table 1. Plasma L-Phenylalanine Levels after L-Phenylalanine Ingestion. Values given are the means \pm the standard deviation, and the ranges, in μ moles per ml. of plasma, found in 19 adult controls and 19 parents (heterozygotes) of known phenylketonuric patients.

	1	Hours after Dose 2	4	Sum of Hourly Levels
Controls:	0.55 \pm .186 (0.30-0.90)	0.55 \pm .168 (0.29-1.02)	0.30 \pm .076 (0.21-0.50)	1.41 \pm .366 (0.87-2.19)
Heterozygotes:	1.14 \pm .187 (0.84-1.44)	1.03 \pm .187 (0.72-1.44)	0.76 \pm .292 (0.45-1.62)	2.93 \pm .458 (2.10-4.02)

Comparison of the two groups on the basis of age, sex, weight, intelligence, or dose per square meter of body surface failed to reveal discrepancies which could account for the observed differences between the phenylalanine plasma levels of the groups. The possibility was exceedingly small that such a difference could have occurred by chance (p less than 0.0001). The excretion of phenylalanine during the nine hours following the oral dose was determined in about half of the individuals. The amounts excreted were not different in the two groups and were insignificant in relation to the amounts disappearing from the blood during the test period. Phenylpyruvic acid in the urine during the same period was never found in the controls and only in one heterozygote who also showed the highest observed plasma levels of phenylalanine. The most probable interpretation of these results is that the heterozygotes as a group have significantly less than the normal phenylalanine oxidizing enzyme activity.

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PRELIMINARY TWIN DATA ON THE SALIVARY EXCRETION OF A RECEPTOR-DESTROYING ENZYME ¹

By C. W. JUNGBLUT, F. J. KALLMANN, B. ROTH
and H. O. GOODMAN

The twin family data presented in this report are concerned with the quantitative excretion patterns of a salivary enzyme, discovered by *Jungeblut, Horvath, and Knox* in 1952 [1]. The enzyme acts on red cells and causes exposure of T antigen on the cellular surface, destroying at the same time hemagglutinating receptors for ColSK virus, a poliomyelitis-like viral agent. The receptor-destroying property of the enzyme is similar to, but not identical with, the RDE principle of cultures of *V. cholerae*.

The enzymatic effect is demonstrable in two ways: (1) by a panagglutination reaction, which depends on the occurrence of hemagglutination when anti-T serum is added to enzyme-modified red cells; (2) by inhibition of viral hemagglutination when ColSK virus is combined with enzyme-modified red cells. Since results obtained by the two methods do not differ and the panagglutination reaction is technically simpler, it has been adopted as the method of choice.

Briefly described, the panagglutination technique is as follows: The supernatant of a centrifuged saliva sample and a series of progressive saline dilutions of saliva are combined, in 0.1 cc. volume, with an equal volume of 0.5 % suspension of washed human O cells. The combinations are placed in the icebox overnight to allow for slow, but complete enzymatic modification of the cells. Following this, 0.2 cc. of a 1:3 dilution of human

¹ Aided by a grant from the Sister Elizabeth Kenny Foundation.

AB serum is added to each sample and the tubes are returned to the ice-box for one hour for cold agglutination to occur. Upon centrifugation and shaking of the sediments, the cells in negative tubes will be found to be in even suspension, while those in positive tubes show clumping of varying degrees.

Previous studies using this test procedure with healthy individuals as well as with poliomyelitis patients during the acute or chronic stage of their disease yielded the following results [2, 3, 4]:

(1) The quantity of enzyme in the saliva in different individuals varies from amounts so minimal as to be either immeasurable or barely detectable to its occurrence in high concentrations.

(2) With some individuals, daily fluctuations of enzyme quantity may occur over a fixed period of time causing characteristic excretion patterns.

(3) Measurable enzyme amounts are usually higher in persons with a history of paralytic poliomyelitis than in persons without such a history.

(4) The presence or absence of the enzyme is unrelated to the bacterial oral flora or to any other extrinsic factor connected with the personal habits of the individual.

In view of these findings the question of possible genic control of the variations in the excretion of the enzyme arose. It was therefore decided to study the excretion patterns of twins, both normal and schizophrenic, and to compare the respective twin data with those obtained on their parents and sibs. The analysis was extended to schizophrenic twin family units in order to investigate whether any correlation existed between salivary enzyme excretion and constitutional defense mechanisms of the central nervous system against non-infectious injury.

The series of normal twin families came from school populations in New York City, Westport, Connecticut and Lansing, Michigan. The abnormal series was taken from family units with an early schizophrenic psychosis in one or both twins. The normal series consisted of a total of 87 persons, including 8 one-egg and 6 two-egg pairs of twins, and the psychotic series of a total of 58 individuals, including 5 one-egg and 6 two-egg pairs of twins. Zygosity diagnosis for each twin pair was based on measurements of common physical characteristics, comparison of blood group factors and fingerprints.

For the purposes of this preliminary report, saliva specimens were collected daily from each person on 5 successive days. Each specimen was tested for enzymatic activity in undiluted saliva as well as in serial two-fold dilutions from 1:5 to 1:160. Positive results were scored by assigning a value of 1 to a reaction which occurred in the undiluted specimen only

and values of 5, 10, 20 and so forth were given to terminal reactions observed in correspondingly higher dilutions. The absence of a reaction with undiluted saliva was scored zero. An average of the five-day-titers was calculated for each person and the figures were entered as "mean RDE reaction" in a tabulation of the data.

When mean RDE reactions of normal and schizophrenic twin family groups are compared (fig. 1), it will be observed that zero reactions occurred in nearly one-third of the normal group, but in less than one tenth of the persons belonging to schizophrenic twin families. In other words, the schizophrenic group showed a definite shift toward higher RDE values, even though many persons included in this group were free of clinical symptoms of schizophrenia.

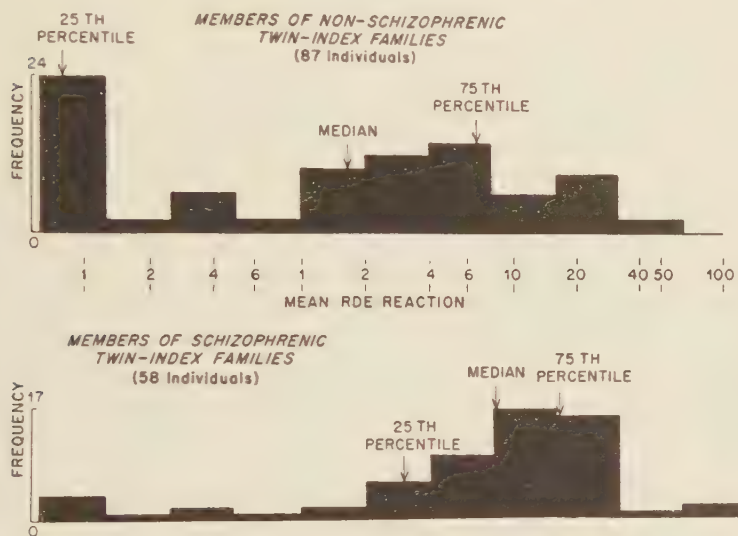


Fig. 1. Distribution of mean receptor-destroying-enzyme. Reactions of members of twin index families (RDE reactions on logarithmic scale).

The actual differences in the quartile distributions of the two groups are presented in table 1. It will be seen that a mean RDE score of 3.0 which occurs at the 25th percentile of the abnormal group, demarcates 60 per cent of the normal group. This finding would indicate that members of schizophrenic family units, like persons with a history of paralytic poliomyelitis, are characterized by the fact that their mean RDE reactions are higher than those of persons without evidence of either disease.

Table 1. Quartile distribution of mean receptor-destroying-enzyme reactions.

	Mean RDE reactions		
	Total population	Psychiatric classification Normal	Schizophrenic
25th Percentile . .	0.4	0.0	3.0
50th Percentile . .	3.8	1.65	8.2
75th Percentile . .	11.0	6.65	16.2
Number of subjects	145	87	58

In order to evaluate similarity or dissimilarity of RDE scores of twins in relation to zygosity, parental RDE scores, and concordance or discordance as to schizophrenia, all members of complete family units were classified as low, medium, or high excretors according to whether their mean RDE reaction was zero, between 0.1 and 8.9 or 9.0 and above. This analysis revealed that in the normal group, all 8 one-egg pairs were similar, whereas 3 of 6 two-egg pairs were dissimilar. If normal and abnormal pairs are taken together (Table 2), similarity occurred in 12 of the 13 pairs (92.3 per cent) of the one-egg group and in 5 of 12 pairs (41.7 per cent) of the two-egg group, a statistically significant difference. It may be added that in the only one-egg pair classified as dissimilar, one could not be entirely sure of the reliability of the sample submitted due to the total deafness and advanced mental deterioration of one twin brother. Our findings point to a possible genetic determination of RDE levels, in addition to the affect which the presence of schizophrenia may have had on the quantitative excretion patterns.

Table 2. Similarity and dissimilarity for low, medium and high RDE excretion in monozygotic and dizygotic twin pairs.

Twin pairs	Totals	Similar	Dissimilar
Monozygotic	13	12 (92.3%)	1 (7.7%)
Dizygotic	12	5 (41.7%)	7 (58.3%)

The genetic theory is strengthened by a comparison of the RDE test scores of twins with those of their parents (Table 3). It will be noted that normal one-egg twins do not differ in their RDE classification, even though their parents may show differences in that respect. By contrast, normal

Table 3. Occurrence of H (high), M (medium) and L (low) reactions in twins as compared with the reactions of their parents.

Number of Families	RDE Reaction of Parents	Zygoty of Twins	Psychiatric Classification	RDE Reactions in Twin Pairs		
				H	M	L
3	HM	DZ	Normal	H M H M M M		
2		MZ	Normal	H H M M M M		
4		DZ	Schizophrenia	(H)(H)(H)M*(H)M(H)M		
1	MM	DZ	Normal			L L
3		MZ	Normal	M M M M L L		
1		DZ	Schizophrenia	(M) M		
1	ML	DZ	Normal	M L		
3		MZ	Normal	M M M M L L		
1		DZ	Schizophrenia	(M) L		
1	LL	DZ	Normal	L L		
5	?	MZ	Schizophrenia	(H)(H)(H)H*(H)(H)(H)(H)(H)M		

○ = Clinical schizophrenia * = Tentative diagnosis of schizophrenia

two-egg twin pairs seem to fall together into the low category only when both parents are low, too. Where both parents are either medium excretors or are in different categories, two-egg twins show correspondingly dissimilar RDE classifications. Unfortunately, there is no family unit in our series where both parents are high excretors.

The relationship between high RDE test scores and schizophrenic symptoms suggested by the crude data mentioned before is also indicated by the distribution of mean RDE values in twin pairs concordant or discordant as to an early form of schizophrenia. Thus, in both zygoty groups, medium or high reaction scores appeared to be associated with schizophrenia. Even more striking is the fact that in 3 of 4 discordant two-egg pairs, it is the schizophrenic twin who is the high or higher reactor. On the whole, one gains the impression that the same differentiating principle, which separated normal and abnormal family groups, tends to express itself in the distribution of concordance and discordance as to schizophrenia in the twin pairs.

Our series are numerically too limited to draw any final conclusions but the trend of the reported data is consistent with the assumption that graded variations in quantitative excretion patterns of the salivary receptor-destroying enzyme are produced by a polygenic type of inheritance.

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HEREDITARY DISORDERS OF THE SKIN

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GENETIC ASPECTS OF PSORIASIS

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Almost all authors studying the genetic aspects of psoriasis agree on the relative frequency of its familial incidence. This incidence has led them to assume that genetic factors play a role in the etiology of this dermatosis. No agreement, however, has been reached on the mode of inheritance which prevails in psoriasis and the interpretations of the observations are as far apart as monofactorial dominance and digene recessivity (*Hoede, Romanus, Steinberg* and collab.).

A review of our own material (243 cases) reveals that among 239 consecutive, non selected, patients suffering from psoriasis 43, i.e. 17.9 per cent were familial cases having one or more than one additional member in their families affected with psoriasis. Familial involvement becomes even more impressive if we go into the number of affected individuals in each family. We found in our material 80 secondary cases in these families; that means that including the 43 index cases in each of these families about 3 individuals on the average were affected. For two reasons these figures may be too low: a certain proportion of the younger members under observation might still develop psoriasis at a later date and a number of less severe instances of psoriasis among the older generations may not have been noted. The figure of 18 per cent of familial cases corresponds well with the figures in the literature amounting to 15-30% of familial cases according to the various authors some of whom found even higher percentages, so *Hoede* 39 per cent and *Lerner* 42 per cent. In view of these figures the familial occurrence of psoriasis cannot be a mere coincidence since this disorder has been found to occur only in a small proportion of the general population. Many authors rate the incidence of psoriasis at 1⁰/₁₀₀. *Gahan* by means of a rough estimate arrives at the rather high rate of 1%; however, *Romanus* agrees with the

figure of $1\frac{0}{00}$, a result which is based on a survey of 132,675 elderly people who were above the average age for the onset of the dermatosis.

Far more complicated than the determination of the familial incidence is the determination of the mode of inheritance of psoriasis. The majority of authors (*Hoede*, *Romanus*, *Lerner* and others) consider psoriasis to be due to a single dominant factor with low penetrance. However, *Steinberg* and collab. contributed important arguments in favor of a recessive mode of inheritance. Our material consists of the above-mentioned 239 families and 4 extensively studied pedigrees dealing with families not included in the consecutive series. In accordance with other recent authors we have not found in our material significant differences between the number of male or female victims of the disease. In addition, males as well as females transmitted the disease to their offspring.

We observed two instances of direct inheritance of psoriasis through 4 generations and two instances of direct inheritance through 3 generations, facts which suggest simple dominance. There were no consanguineous marriages in these families. Instances of direct inheritance of psoriasis through 4 generations have been repeatedly reported in the literature: it, therefore, seems that the dominant mode of inheritance has been established for a number of cases. However, in the great majority of pedigrees skipping of generations is the rule, also the number of probands having an affected parent is in most statistics strikingly low such as around 8 per cent in *Hoede's* as well as in *Romanus'* series. It is only slightly higher in our material: 25 of the 239 non-selected probands, that is 10.5 per cent, have at least one affected parent.

The relative number of affected siblings is low, too. Applying *Weinberg's* proband method for siblings whose age is over 30 years *Romanus* finds about 9 per cent of these affected. *Steinberg* is so far the only author who has evaluated the sibships separately for the offspring of matings of two non-affected and of an affected with a non-affected parent which is, of course, an indispensable device for the analysis of inheritance patterns. With correction for the age of manifestation of the disorder he finds in the first group five per cent and in the second group 22.1 per cent of affected siblings. These figures have led *Steinberg* to the ingenious hypothesis of digene recessive inheritance. This theory, however, leaves no explanation for the not infrequent occurrence of direct inheritance of psoriasis through 4 generations. Moreover, *Steinberg's* figures would in view of his hypothesis correspond to a high penetrance of 80–88 % which seems contradicted by the low incidence of psoriasis among the offspring of matings of two affected individuals.

Romanus collects 30 families where both parents were affected from the literature with particular attention to five such matings which produced children who lived to adult age. There were 14 children of whom only eight were affected, assuming recessivity, this would denote a penetrance of only 57%. *Romanus* does not give exact figures of his own pertinent observations, but he emphasizes that there were not more affected individuals among the children of two affected parents than among those of one affected and one non-affected parent. This fact strongly militates against the assumption of a digene recessive mode of inheritance with high penetrance. It does not exclude, however, recessive inheritance with a low manifestation rate. Our own material includes two matings of two affected parents. In one of them the children are still too young to be considered as definitely negative; the second one deserves particular interest. Among five children ranging in age from 22 to 35 years only two are affected, the oldest and the fourth one. This fourth child, a 27-year-old son exhibits a severe, generalized form of psoriasis, quite different from that of his parents and sister. It seems plausible that this individual may represent the homozygous state of a dominant gene for psoriasis.

With this observation in mind, we reviewed the severe, generalized cases occurring in our pedigrees. We found three additional such cases. One was suffering from severe, generalized psoriasis since her 6th year. Her mother was a psoriatic; so was a paternal aunt; the possibility that she is another example of the homozygous state of the irregularly dominant gene is, therefore, high. In another instance the only son of a marriage of second cousins suffered from generalized, severe psoriasis. Whether the consanguinity of the parents plays a role in this case, cannot be decided; however, psoriasis definitely occurred in the families of both parents of the patient suffering from the generalized disorder. The mother's father as well as a half-brother of the patient's father suffered from the dermatosis. Here again the marriage of two persons from families in which psoriasis is present may have led to the homozygous state of the gene in the son. In our last generalized case the father had psoriasis, but it is not known whether the dermatosis occurred in the mother's family.

Our observations point to dominant inheritance with generally low penetrance for a number of cases. Two facts, however, apparently do not fit into this assumption. One is the comparatively high concordance rate in monozygotic twins, contradicting the low penetrance. Collecting records of twin pairs suffering from psoriasis from the literature and adding an observation of his own, *Pfändler* found among 16 monozygotic pairs 11 concordant and only 5 discordant. The other important argument against

dominance is the finding of *Steinberg* and collab. that there are more affected individuals among the offspring of matings of an affected with a non-affected parent than of matings of two non-affected parents. It is, further, striking that in certain families dominance is obvious and regular while in others throughout the entire pedigree penetrance is low. It might be conceivable that to a certain extent also the degree of penetrance of the pathologic factor is genetically determined, either due to modifiers or some other genetic mechanism. This would mean that there is more than one gene involved. Another, perhaps more plausible explanation which was considered already by *Steinberg* and collab. would be that the genotypical representation of the predisposition to psoriasis is heterogeneous, consisting in some cases of a recessive mutant gene or genes, and of one or more dominant factors in other cases.

In this connection we may recall that recent investigations have succeeded in clarifying apparent discrepancies in the mode of inheritance of two well-known hereditary pathologic conditions, gout and congenital dislocation of the hip. Apparent irregularities of the dominant inheritance of gout disappeared when systematic examinations of the blood of all family members revealed that a number of them, though clinically healthy, presented a hyperuricemia. For the congenital dislocation of the hip a recessive mode of inheritance had seemed most probable years ago and one of us (B.M.A.) in 1928 went so far as to assume digene recessivity. However, more recent systematic X-ray studies in the families of such patients have demonstrated that a number of clinically normal family members displayed dysplasia of the hip radiographically. This dysplasia is dominantly inherited. A similar situation might exist in psoriasis. *Monacelli* and *Ribuffo* e.g. have found in normal sections of the skin of psoriatic patients localized disorders of the carbohydrate metabolism which were not combined with any generalized metabolic disorder. If future investigations will demonstrate characteristic chemical changes in the skin of psoriasis patients, it might be well worthwhile to investigate the families of such patients systematically in this direction.

For many years one of us (P.G.) has been giving particular attention to the occurrence of diabetes mellitus in psoriatic patients or in their families. Including our secondary cases, we found that 19 out of 333 psoriatic patients (index plus secondary cases) were suffering from diabetes mellitus. This means that diabetes occurred in 5.7% of our psoriatic patients. In 13 of these 19 cases the diabetes affected more than 1 member of the family. In addition, 23 of our psoriatic patients had one or more than one diabetic in their families who, however, were free from psoriasis.

In other words: among 243 families with at least one psoriatic patient we found 42 i.e. 17.3 % which included one or more than one family member suffering from diabetes regardless of whether this disorder occurred in a family member affected by psoriasis or not. The figure of 5.7 % of psoriatic patients suffering from diabetes as compared with the incidence of diabetes in the general population (1 %) is significant at the .01 level. We have to consider, however, that there were among our patients only a small number below 20 years, that about 43 % of them were between 30 and 49, and 28 % between 50 and 69 years. This means that our material leaned towards a higher age group in which diabetes is more frequent than in the population in general. Since, however, according to *Joslin* even in the age group of 55 to 64 years only 1.5 % of all individuals are diabetics, we may assume that the figure of 5.7 % for our psoriatic population is significant. The evaluation of the incidence of diabetes in the families of a control population consisting of individuals without chronic skin affections will show to what extent the incidence in the families of our psoriatic patients is significant.

There is apparently no pathophysiologic mechanism which could explain the connection between the two disorders; such a relationship is also highly improbable since the great majority of diabetics never develop psoriasis, and the majority of psoriatics do not suffer from diabetes, and there may be an interval of many years between the onset of the two diseases in individuals suffering from both of them. Since a pathogenetic relationship seems to be excluded, it appears most probable that both diseases have some causal factor in common. In view of the fact that both diseases are genetically determined, the common denominator will most probably lie in the genotype, a theory which has been corroborated by the fact that we may find in the same family besides individuals suffering from psoriasis alone, others suffering from diabetes alone, and still others suffering from both diseases. In view of the fact that both diseases occur combined only in a small part of the cases, the assumption of a single pleiotropic factor as their cause is highly improbable. It seems, however, possible that there exists a closer connection between the mutant genes causing the two diseases. The present material does not offer proof of this possibility.

Attention was also given to the combination of psoriasis with chronic arthritis which is considered by many authors as frequent (*Ingram*). In the great majority of cases it is the rheumatoid type of chronic polyarthritis which in combination with psoriasis has been called arthritis psoriatica. Among our index cases 43, i.e. 17.7 % suffered from arthritis; if we consider all our psoriatics, index plus secondary cases, this ratio is 52 : 333, i.e. 15.6 %; in ten additional cases arthritis occurred in non-psoriatic family members of

our index cases. Here again each of the two disorders occurs far more frequently alone than in combination with the other one which militates against the assumption of a pathogenetic connection. *Bauer* and *Vogl* in an analysis of their pedigrees have pointed out that the common denominator may be a genopathy involving mutant genes which play a role in the etiology of both disorders. Our observations do not yield any new clues as to the character of this relationship. A careful statistical analysis of an appropriate control population would be necessary to decide how far our figures concerning the combination of the two diseases are significant.

In *conclusion* our observations support the assumption of a hereditary predisposition to psoriasis. The genotypic representation of this dermatosis is apparently heterogeneous. In a number of cases, however, the predisposition to psoriasis seems to be caused by a dominant mutant gene which in its homozygous state appears to determine the generalized, severe form of the dermatosis. There exists, furthermore, a relationship between the two hereditary conditions of psoriasis and diabetes mellitus: the possibility of a genotypic correlation between the two diseases is considered.

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Discussion

G. Lomholt (Copenhagen): Talking about genetic aspects of psoriasis I want to draw attention to a census investigation I made a few years ago on the Faeroe-Islands in the North Atlantic, a very isolated part of the Danish Kingdom.

The Faeroe Islands have a population around 30,000 inhabitants. The climate is very rainy and foggy. Their sunny days are few. Their food is fatty and includes very few

vegetables. These circumstances are generally considered to be very unfavourable for patients with psoriasis.

The advantage to investigate an island population when hereditary problems are concerned is evident. People move very seldom, and the chance to find nearly all relatives in the examined area is very great.

I have examined the total population in one third of the Islands—a total of 11,000 persons concerning dermatological diseases and especially psoriasis and its heredity. I visited every house in the area. I found a total of 312 patients with psoriasis, 158 males and 154 females. That is the same incidence in both sexes.

The investigation covered all cases, specially including patients who would not normally seek medical advice. The material also includes 11 per cent without symptoms at the time of investigation, persons giving exact informations and description of former manifest psoriasis.

The incidence of the disease on the Faeroe Islands was found to be nearly 3 per cent (2.84).

I am able to demonstrate many comprehensive genealogical tables concerning the families up there, but lack of time in a short contribution to discussion makes this impossible. The greatest of this tables includes 27 cases of psoriasis distributed over five generations.

Psoriasis is found to be inherited dominantly with failing manifestation. The manifestation probability is calculated to about 40 per cent.

H. Dorn (Berlin): Wir beobachteten in der Zeit von 1953–1955 an der Hautklinik der Freien Universität Berlin 312 klinische Psoriasisfälle, von denen 124 = 41% größtenteils über mehrere Generationen erblich sowie 188 = 59% nicht erblich – sporadisch – waren. Eine hauptsächliche Voraussetzung für die psoriatische Eruption sind ein potentiell psoriatisches Individuum sowie ferner ein innerer oder äußerer Anstoß zur Manifestation. Als mögliche auslösende Ursachen fanden wir zu 26,6% eine Angina in der Anamnese, zu 7,05% eine Assoziation zwischen Psoriasis und der Gruppe der rheumatischen Erkrankungen, zu 3,84% die Entwicklung der Psoriasis aus einem Ekzem. Als Begleiterkrankung fanden wir nur zu 1% ein Diabetes mellitus, ein Zusammenhang zwischen endokrinen Störungen (Adipositas, Struma) und Psoriasis bestand zu 5,12%. Zu 3,2% fanden wir die Psoriasis bei Fleischern und zu 0,64% bei Landwirten.

Zu beachten ist unbedingt die Psoriasisanfälligkeit infolge des Vorliegens nervaler Faktoren, welche durch pathologische, corticovasculäre Reflexe ausgelöst werden und sich vor allem an den Hautgefäßen manifestieren (Acetylcholinvermehrung).

Grundsätzlich sollte man die Psoriasis, bei der die einzelnen Faktoren der Peristase eine große Rolle spielen und bei der unter der Voraussetzung einer exakten Erhebung der Familienanamnese über mehrere Generationen die nachweislich 41% hereditären Fälle mit einem monofaktoriellen, unregelmäßig dominanten Erbgang eher ein Minimum als einen Maximalwert darstellen, den erblichen Hautleiden zuordnen.

A. A. Messer (New York): Much of the data summarized in this paper concerning Genetic factors in psoriasis appears to be contradictory. Dr. *Aschner*, as well as the other authors quoted, point to unknown factors in the genesis of the disease.

I should like to ask Dr. *Aschner* her opinion as to psychodynamic factors being pre-dominant here. If we look at the skin as being the first organ with which the individual comes into contact with the environment, then psoriatic lesions could represent a manifestation of the earliest difficulties.

In terms of the parent-child relationship, certainly an individual who has experienced significant emotional trauma in this area would be bound to reflect the same in handling his or her own offspring.

I note also that the first discussant in presenting his findings, took great pains to point out the difficult environment to which the individual had to adapt.

B. M. Aschner (New York): Dr. Lomholt's observations appear particularly interesting; they show clearly that psoriasis occurs in males and females with equal frequency as assumed by most recent authors in contradiction to earlier investigators. As we have mentioned the penetrance of the mutant gene or genes causing a predisposition to psoriasis is rather low; therefore, it is not surprising that various environmental factors such as infections or also psychodynamic traumas play a role in the actual manifestation of the dermatosis. This does not disprove the genetic origin of psoriasis. As a rule, affection of mother and child cannot be explained by psychosomatic factors since the children may develop the dermatosis late in life, long after the death of their mother.

Schnyder, U. W., and D. Sommacal-Schopf: *Acta genet.* 7, 204-206, 1957

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FOURTEEN CASES OF ERYTHRO-KERATODERMIA FIGURATA VARIABILIS WITHIN ONE FAMILY

By U. W. SCHNYDER and D. SOMMACAL-SCHOPF

In this paper, we deal with a strange congenital Erythro-Keratoderma, which was described first in 1909 by *Nicolas* and *Jambon*. This affection is characterized on the one hand by a progressive growth of the foci and, on the other, by their partial or total regression. The clinical and histological aspects of this rare dermatosis have since been described in detail by *Budlowsky*, *Froilano de Mello*, *Jeanselme*, *Chevallier*, *Burnier* and *Perrin*, *Mendes da Costa*, as well as *Miescher* and *Stäheli*. At the 37th Meeting of the Swiss Dermatological Society, we had the occasion to present another case of Erythro-Keratoderma Figurata Variabilis. This interesting case induced us to undertake an investigation of the whole family of this patient and, to our surprise, we were able to discover thirteen further cases of the same dermatosis—7 females and 6 males—distributed over 4 generations (see

figure 1). This family originates from the region of Wattwil in the Toggenburg (Switzerland). The cases 1 to 6 (marked with a cross) were examined by the authors personally. The diagnosis of cases 10, 11, 13 and 14 (marked with a double dash) has been confirmed by medical records and family-pictures, while the diagnoses of cases 7, 8, 9 and 12 could be established only on the basis of accounts and descriptions given us by living members of the family.

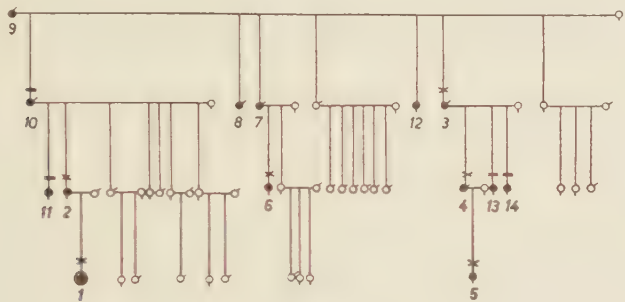


Fig. 1.

A study of the literature reveals that hitherto there have been publications concerning single cases or several cases involving parents and children only, but never, as far as we could ascertain, have investigations been undertaken concerning several generations of such a family. Thus, *Mendes da Costa*, *Rille* and *Budlovsky* described the simultaneous appearance of *Keratoderma Figurata Variabilis* in one parent and a child, *Nakao* in a father and two children, *Goldschlag* in a father and three children, *Hermans* in a father and six children, *Jeanselme* and *Miescher* each in two sisters, *Froilano de Mello* in three sisters. These authors do not agree about the mode of inheritance, most of them considering it dominant, while a few regard it as recessive.

We were, however, compelled to the conclusion, on the basis of the analysis of 14 cases extending over four generations of the same family, that the *Erythro-Keratoderma* in this family shows regular dominant heredity, as the disease appears in all the four controlled generations, though only in those family-members who descend from one affected parent. We could not find any anomalies in this family in addition to the congenital dermatosis; there is no incest. In our opinion therefore, we deal with a monohybrid hereditary disease.

In our cases, we found it also particularly interesting that the morphological expression of the disease was subject to such variation in the different members of this family. Thus, case 3 and his descendants show mainly the erythrodermatic symptoms characterized by their great variability. The red macules are fugitive; they come and go within hours or days. They are often caused by changes in weather and temperature and use of soap and water, and they may appear also premenstrually. Case 6 emphasized that the red macules appear always in the same localization and in more or less the same shape and extension. Case 3 said that his red macules exceptionally, persist for days and weeks, take on a greyish, then a more brownish colour, and eventually become firmer resembling more and more the keratotic lesions. As this change from erythrodermatic into keratotic lesions has been observed by only this case, actually an elderly man who had difficulties in giving us an exact account of his symptoms, we did not feel quite sure about the trustworthiness of his description in this particular point.

As opposed to case 3 and his children, in case 10 and his descendants, the dominant feature of the dermatosis is the Keratodermia, which is quite constant as regards shape, intensity, and extension, all subject to slow changes only within months and years.

Budlovsky observed in her cases also this division of the dermatosis into either more characteristically keratotic lesions or more characteristically erythrodermatic lesions, and therefore proposed to name the disease *Kerato et Erythrodermia Figurata Variabilis*.

It therefore follows that the Keratodermia is obviously the constant element of the dermatosis whereas the erythrodermatic symptoms are of a fugitive nature. Thus, apart from the dominantly inherited, idiotypic predisposition there appear to be exogenous factors that are responsible for the manifestation of the erythrodermatic lesions of the dermatosis.

Summary

Report on 14 cases of Erythro-Keratodermia Figurata Variabilis distributed over four generations of the same family showing regular dominant inheritance.

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RECHERCHES SUR L'HÉRÉDITÉ DE L'ÉPITHÉLIOMA ADENOÏDES CYSTICUM

Par A. SERRA, M. G. BERNARDI-RONZONI et R. PAOLETTI

Maladie très rare et cependant répandue parmi plusieurs populations blanches et noires, l'*epithelioma adenoides cysticum* se caractérise, dès l'époque de sa manifestation – enfance ou puberté –, par de petites tumeurs bénignes de la peau, isolées parfois, mais le plus souvent concentrées et disposées symétriquement autour des ailes du nez, de la bouche, des oreilles, sur le front, sur le cuir chevelu, et quelquefois même sur le tronc et les membres. L'étude histologique de ces tumeurs découvre une prolifération des cellules basales de l'épiderme et des follicules pileux. De cette manière se forment des nids de cellules amitotiques évoluant fréquemment en kystes. Rarement on a aussi observé une dégénération maligne de ces tumeurs.

On ne connaît aucun facteur étiologique spécifique. Cockayne [1928, 1933], Fliegelman et Kruse [1948] et Scott [1953] ont proposé l'hypothèse d'un facteur héréditaire dominant, ou probablement dominant.

Il nous a été donné de recueillir, à partir d'un sujet diagnostiqué de manière sûre à l'Hôpital «Maggiore» de Milan, une généalogie de 290 sujets. Celle-ci englobe très probablement tous les cas de la maladie survenus dans le territoire d'Abbiategrosso (Milan) en Italie, au cours du siècle dernier. Nous avons examiné personnellement tous les individus vivants. Les renseignements concernant les individus morts furent obtenues chez plusieurs membres de la famille et contrôlés par recoupement. Souvent ils furent confirmés par des photographies.

Les 48 cas de maladie découverts ainsi, répartis dans trente familles, nous ont paru suffire à l'examen et la discussion génético-statistique du mode de transmission de cette forme de néoplasme bénin.

Nous ne donnerons ici que les conclusions brièvement commentées. Pour une discussion plus exhaustive, nous renvoyons à notre travail in extenso*.

1. L'hypothèse génétique la plus vraisemblable sur le mécanisme de transmission de l'épithélioma est celle de la dominance. D'une part se vérifie le critère fondamental de dominance, c'est-à-dire la transmission directe du caractère d'un sujet atteint avec continuité à d'autres sujets atteints; et d'autre part il est impossible d'accorder les faits observés à l'hypothèse de la recessivité, suggérée par la présence de quatre familles qui descendent de parents phénotypiquement normaux. En effet on devrait admettre qu'au moins les $33,8 \pm 5,9\%$ de la population dans laquelle les individus de la lignée ont pris leur conjoint sont hétérezygotes pour le facteur en question. Par conséquent 2% ou moins seraient homozygotes pour le même facteur, c'est-à-dire malades. A ceci s'oppose le fait d'observation que la maladie en question est très rare.

2. Toutefois l'hypothèse d'une simple dominance monogénique à deux allèles ne peut être retenue, ainsi que le montre le test de χ^2 comparant les distributions observée et théorique de la descendance de 30 couples de même combinaison matrimoniale ($DR \times RR$). Ces trente couples avec leur

Tableau 1. Distribution des fratries (n) selon le nombre de sujets et le nombre de sujets atteints.

Nombre de sujets atteints (a)	Nombre de sujets dans la fratrie (s)										Total
	1	2	3	4	5	6	7	8	9	10	
0	6	2	1	—	—	—	—	—	—	—	
1	—	4	2	1	2	—	—	—	—	—	
2		—	1	1	—	—	—	1	1	—	
3			—	1	—	1	—	—	2	—	
4				—	—	—	1	—	1	1	
5					—	—	—	—	—	—	
6						—	—	—	—	—	
7							—	—	—	1	
Σn_{sa}	6	6	4	3	2	1	1	1	4	2	30
Σan_{ss}	—	4	4	6	2	3	4	2	12	11	48
Σsn_{ss}	6	12	12	12	10	6	7	8	36	20	129

* Le travail in extenso va paraître dans *Acta Geneticae Medicae et Gemellologiae*.

descendance, qui font partie de notre matériel, peuvent être considérés comme un ensemble représentatif de familles atteintes ou pouvant avoir des descendants affectés par la maladie (Tab. 1). Le rapport «sains : malades» observé diffère de façon statistiquement significative du rapport 1 : 1 que prévoirait la théorie ($\chi^2 = 8,442$; $N = 1$; $0,01 > P > 0,001$) (Tab. 2).

3. Mais une analyse plus poussée de ce test de χ^2 (Tab. 2) montre que l'incidence de la maladie n'est pas la même dans les deux sexes. Pour les hommes la fréquence observée diffère très significativement de la fréquence théorique calculée (sur 75 sujets mâles, 22 – c'est-à-dire 29,3 % – sont atteints: $\chi^2 = 12,814$; $N = 1$; $P < 0,001$). Par contre pour les femmes l'accord est très bon entre les deux valeurs (sur 54 femmes, 26 – c'est-à-dire 48,1 % – sont atteintes: $\chi^2 = 0,074$; $N = 1$; $0,80 > P > 0,70$). Il est à noter que cependant la «sex-ratio» ne s'éloigne pas significativement de la normale. On peut donc conclure que le facteur héréditaire n'a pas une dominance régulière.

Tableau 2.

Sexe	Sujets			χ^2
	atteints	sains	total	
Hommes	22	53	75	12,814
Femmes	26	28	54	0,074
Total	48	81	129	8,442

	χ^2	N	P
Total	12,888	2	
Déviation	8,442	1	$0,01 > P > 0,001$
Hétérogénéité . . .	4,446	1	$0,05 > P > 0,02$

4. Il ne semble pas que cette irrégularité doive être attribuée à une liaison partielle ou absolue avec le sexe. Elle ne peut être totale, parce que de pères atteints proviennent, contrairement à ce qu'on attendrait, non seulement des filles atteintes, mais aussi des fils atteints. Elle n'est pas non plus partielle: parmi les descendants des pères malades qui tous ont reçu le gène de la grand-mère, le nombre des filles atteintes est sensiblement augmenté tandis que le nombre des fils atteints est diminué; cependant on ne peut conclure avec certitude que l'écart transgresse les limites du hasard

($\chi^2 = 3,832$; $N = 1$; $P \simeq 0,05$). D'autre part, la déviation par rapport à la relation 1 : 1 reste significative pour les sujets mâles même chez les descendants des mères atteintes ($\chi^2 = 6,480$; $N = 1$; $P \simeq 0,01$).

5. Bien plus probable, au contraire, semble l'hypothèse que l'irrégularité dans la dominance puisse être attribuée à une pénétrance du gène qui diffère selon le sexe. Une mesure approximative de la pénétrance, estimée d'après notre matériel, nous donne les valeurs de $70,0 \pm 14,5\%$ pour les hommes, et de $91,7 \pm 7,8\%$ pour les femmes. Supposant alors que ces valeurs représentent des moyennes approximatives de pénétrance respectives des deux sexes, on peut estimer *à priori* les nombres attendus de fils et de filles atteints, dans l'hypothèse de la dominance du facteur. Un test de χ^2 permet de comparer ces valeurs théoriques aux nombres observés (Tab. 3 et 4). L'accord avec la prévision, tant pour les hommes que pour les femmes, semble en faveur de l'hypothèse avancée.

Tableau 3.

	atteints	sains	Total
Observés	22	53	75
Attendus	26,25	48,75	75
$\chi^2 = 1,059$	$N = 1$		$0,50 > P > 0,30$

Tableau 4.

	atteintes	saines	Total
Observées	26	28	54
Attendues	24,84	29,16	54
$\chi^2 = 0,100$	$N = 1$		$0,80 > P > 0,70$

En résumé:

L'action d'un facteur héréditaire dans la transmission de l'*epithelioma adenoides cysticum* est démontrée.

Ce facteur semble bien pouvoir être considéré comme dominant autosomal monomérique.

Mais sa manifestation est irrégulière à cause d'une moindre pénétrance du gène chez les sujets mâles.

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A CASE OF GENERAL ALBINISM

By Thras. VLISSIDIS

In a previous communication [1] a case of albinism in two young brothers was presented together with an analysis of the genealogic tree.

Further investigations have shown that the father of the two young men with albinism has a daughter without any signs of albinism in an other marriage.

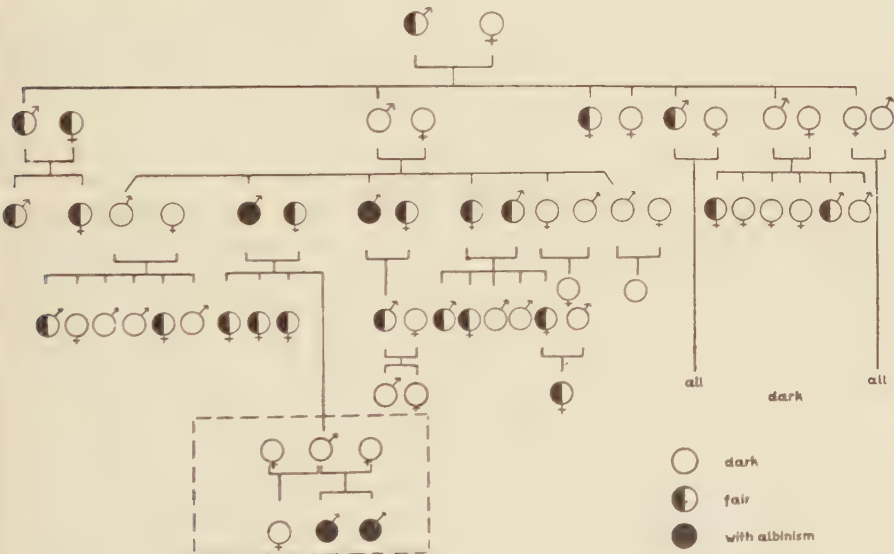


Fig. 1. General Albinism.

A case of hereditary black spots on the skin

A case of hereditary black spots in four generations is presented. As is evident from the genealogic tree the black spots appeared in the F₁. But

since then they have appeared constantly in every generation, although on various parts of the body; thus in the F_1 they appeared on the left shoulder, in the F_2 on the left cheek, and in the F_4 on the left leg.

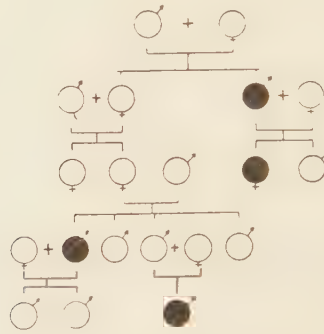


Fig. 2. Heredity of black spots.

The hereditary nature of the phenomenon is evident. The mode of inheritance may be dominant, possibly autosomal.

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INHERITANCE OF CONGENITAL MALFORMATIONS

Kherumian, R., M. Durand, C. Metianu, J. Moullec et Odette Kherumian-Allary: Acta genet. 7, 213-214, 1957

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LE PROBLÈME DE L'ÉTIOLOGIE GÉNÉTIQUE DES CARDIOPATHIES CONGÉNITALIS

Par R. KHERUMIAN, M. DURAND, C. METIANU,
J. MOULLEC et Odette KHERUMIAN-ALLARY

L'étude systématique des cardiopathies congénitales par notre équipe de généticiens et de cardiologues, nous a conduit à la conclusion que les facteurs exogènes, dont notamment la rubéole maternelle du début de la grossesse, n'expliquent qu'une très faible partie de ces malformations.

L'examen des proches des cardiopathes congénitaux (pères, mères, frères, sœurs, etc.) a révélé une concentration, hautement significative, dans ces familles de tares et affections les plus diverses: pieds bot, imperforation de l'anus, spina bifida aperta, obésité, dysendocrinie, agénésie rénale, hypotrophie staturale, amputation congénitale de la main, luxation congénitale de la hanche, hypospadias, myopie congénitale, nystagmus, épilepsie, arriération mentale, troubles psychiques divers, etc., sans compter une grande fréquence de décès subits, d'hypertension, de diabète, etc.

Il s'en dégage une impression de lignées véhiculant des gènes «détrimentaux» multiples, c'est-à-dire, de lignées qui diffèrent nettement de la population générale par leur fardeau de tares génétiques.

L'intervention dans la genèse des cardiopathies congénitales de facteurs héréditaires est confirmée par l'étude des fratries. Qu'il s'agisse de fratries examinées par nous ou de fratries recensées dans les dossiers de l'hôpital Broussais à Paris, on trouve que la fréquence des cardiopathies congénitales chez les frères et les sœurs des probands est presque quatre fois plus élevée que dans la population générale à la naissance.

Ces considérations sont confirmées en particulier par des fratries comportant trois cas de cardiopathies congénitales (observées par nous).

Un autre fait semble aussi confirmer l'action des facteurs héréditaires dans la production des malformations du cœur et des gros vaisseaux: c'est la fréquence de jumeaux, généralement dizygotes dans les lignées et dans les fratries atteintes. Cette fréquence est quatre à cinq fois plus élevée que dans la population générale. Il est à noter que les naissances triples observées par nous dans les lignées de nos probands sont environ 10 fois plus fréquentes que dans la population présumée normale.

Nous rappelons en outre une de nos communications antérieures (Congrès d'Anthropologie Différentielle, Mayence 1954) à propos de la grande fréquence de lignes palmaires transverses (lignes simiennes) chez ces malades et chez leurs proches, en particulier du sexe masculin. La fréquence de ce stigmate dans les cardiopathies congénitales est un argument de plus en faveur de leur déterminisme génétique, tout au moins partiel.

A ce faisceau d'arguments, on pourrait opposer des discordances chez les jumeaux monozygotes, observées aussi bien par nous que par divers autres chercheurs. Cependant, l'analyse plus approfondie de ces cas montre qu'il s'agit généralement de dextrocardies isolées ou compliquées d'autres malformations; il s'agirait en quelque sorte du même phénomène que celui qui conduit à la formation de jumeaux en miroir.

Par ailleurs, les discordances chez les monozygotes pourraient s'interpréter aussi comme le résultat du clivage anormal qui détermine la production de vrais jumeaux, mais n'affectant qu'un seul partenaire du couple.

Nous estimons en conséquence que les cardiopathies congénitales résulteraient de l'action de certains facteurs exogènes (qui restent à préciser) sur des génotypes particulièrement vulnérables. Nous ne pensons pas que le substrat héréditaire des cardiopathies congénitales soit du type polygène et nous sommes enclins à croire que l'hypothèse des deux gènes récessifs ou, au maximum, de trois gènes, devrait en rendre compte.

Il va de soi qu'une explication unique de toutes les cardiopathies congénitales n'est guère concevable et que leur interprétation définitive nécessite une ventilation minutieuse des diverses malformations que l'on réunit sous cette étiquette.

Ce résumé anticipant sur des recherches en cours, un exposé détaillé des données observées et de leur signification génétique sera publié *in extenso* ultérieurement.

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ON THE INHERITANCE AND DEVELOPMENT OF PREAXIAL AND POSTAXIAL TYPES OF POLYDACTYLY

By F. DeMARINIS and A. SOBBOTA

Polydactylism is generally defined as a condition of hand and/or foot in which there are more than the usual number of digits. In man 6 fingers are not too unusual, but 7 or more fingers are indeed rare. This digital condition is not peculiar to man but is also found in other vertebrates.

Polydactyly in man may occur in either one or both hands or in one or both feet and often the condition is found in both hands and feet. In the present paper we have distinguished two anatomical forms of polydactyly. Preaxial polydactyly when the extra digit occurs on the thumb side and postaxial polydactyly when the extra digit occurs on the side of the little finger. This brief paper attempts to describe two such types of polydactyly.

The first case is a preaxial polydactyly. This condition was first observed in a new-born baby girl. Both of her thumbs were affected. The left thumb had a definite appearance of duplication which first attracted the attention of the attending doctor. The right thumb was slightly wider in appearance but definitely normal otherwise.

Both parents were examined. The father appeared perfectly normal while the mother showed a slight variation in her right thumb, it curved radially. There is some doubt as to whether this variation constitutes a definite departure from the normal. The radiologists were not in agreement. We consider this condition as affected solely on the basis that the mother is connected with the affected child.

The pedigree in itself is too small to definitely determine the mode of inheritance. However, the general pattern seems to indicate that it may

be inherited as a dominant. The work of *Rudert* [1938] and *Callau* [1942] seems to concur with our opinion.

The second form of polydactyly we wish to present is the postaxial type.

This condition was found in a 44-year-old colored woman. She had a sixth miniature finger arising at the base of the little finger (5th) in both hands. A similar condition occurred on the feet but here the extra toes had been removed by surgery at birth. X-ray examination of the hands reveals the presence of only two phalanges in each of these extra digits. They arise at the site of the metacarpal-phalangeal joint. Further inquiry of this case revealed that this woman has two daughters. The older is unaffected, and the other had had a similar extra digit on both hands like the mother but in a modified form. These had been removed surgically at birth. No polydactylism was indicated in the feet. It is of interest to record that this younger daughter is presently suffering from leukemia and arthritis. It is also of interest to note that both of the mother's parents had this trait on both hands and feet. Yet her two sisters were unaffected. Such a condition indicates that this trait may be inherited as a dominant.

More recent workers in this field, *McClintic* [1935], *Jackson* [1937], *Ordiorne* [1943], and *Johnston and Davis* [1953] are all in agreement that this trait is due to an irregular dominant factor. Our data seems likewise to be in harmony with this point of view. The non-affected children derived from the two affected parents, excludes the possibility that the parents are homozygous recessive. The probability is more favorable that both parents are heterozygous dominant for this trait.

A distinction is made here between preaxial and postaxial polydactyly. From our observations and our survey of the literature we have never come across a pedigree in which the two forms occurred together, that is, one is not a variant of the other. This points of the possibility that each type may be due to a different dominant gene.

Discussion

L. S. Wildervanck (Groningen): I have examined a family in which—dominantly hereditary—several individuals occurred with triphalangeal thumbs. In one individual, the terminal phalanx of the thumb was partially split up, a beginning of polydactyly. So there may be perhaps a connection between triphalangy and preaxial-polydactyly.

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THE PHYSICAL CHARACTERISTICS AND HEREDITY OF SHORT THUMBS

By R. M. STECHER

Congenital short thumbs are so characteristic in size and shape that they can be recognized at a glance. They are of such minor clinical importance that very little attention has been given to them. They are rare enough to be unusual, yet they occur with sufficient frequency to lend themselves easily to genetic study and analysis. Having noted the condition among friends and casual acquaintances, it was decided to undertake a systematic search for additional examples, to estimate their frequency in the general population, to collect pedigrees, to determine the type of inheritance and to compute their gene frequency. The results are reported here.

The author first noted short thumbs in a family gardener forty years ago. His interest was further aroused on noticing a personal friend with one short thumb whose mother was normal but whose grandmother had been affected. Since paying attention to the problem short thumbs have been seen in physicians from Cleveland, London, Edinburgh, Rome and Germany, they have been noted in an elevator operator, a waitress, a chauffeur in Madrid and in natives of Brazil, Peru, Mexico and Korea.

The deformity of the congenital short thumb is confined to the distal phalanx. The distal phalanx is about two thirds the usual length. The shortening also occurs in the distal half of the distal phalanx so that the thumb nail is one half to one third the usual length. The distal phalanx and the nail are both obviously broadened giving the thumb a paddle or a spatula like shape and the terminal segment is thickened. These thumbs have been popularly called potters thumbs. Palm readers think of them as murderer's thumbs. They occur bilaterally in about half the cases, involve each thumb separately in equal numbers and seem to be widely distributed among races and nations. The defect is often recognized at birth. It may not be noted until adolescence. Several women have stated that they always folded

their thumbs under their fingers from the time of their first remembrance because of their ugly appearance. Although present at birth, the deformity becomes more marked until total growth has been attained.

In order to estimate the frequency of short thumbs in the general population surveys were made of patients at Cleveland City Hospital. At various times every patient in the hospital was examined and the condition of each thumb was recorded along with the patient's name, sex, age and race. In order to study the growth and development of short thumbs permission was graciously granted by Dr. Mark C. Shinnerer, Superintendent of Schools of Cleveland and the Cleveland Board of Education to the author to examine primary school children. In this way 9838 people were observed. Of these, 34 were found with one or two short thumbs for an incidence in the general population of 0.35 per cent. There were 32 of 7853 white people affected or 0.41 per cent, 2 of 1985 Negroes or 0.1 per cent, 9 of 4873 males or 0.18 per cent and 25 of 4965 females or 0.5 per cent. Analysing these groups further it was found that there were 7 of 4855 white males affected or 0.17 per cent and 25 of 3798 white females for 0.66 per cent. Only 2 of 818 Negro males or 0.25 per cent and none of 1167 Negro females were affected. Besides the 34 subjects discovered in the survey 61 other subjects were found and studied.

Whenever possible thumbs were measured, photographed and radiographed. Pedigrees were obtained and affected or doubtful relatives seen when possible. Growing children were radiographed at frequent intervals, three to six months, to observe growth of bones and age of closure of epiphyses. At various times the study was expanded to include observations on other fingers, toes, ear lobes, blood groups, interdigital hair, phenylthiocarbimide tasting, not only upon the subjects themselves but also their siblings and their parents. These observations were made in the hopes that linkage might be found.

A total of 95 people with at least one short thumb have been seen and some information obtained about them. These were 33 males and 62 females. The incidence of 2 females for one male is considerably different from the sex incidence found in the survey of the general population of three females (25) to one male (9). Of 95 affected people 18 had short right thumbs, 17 had left thumbs and 60 had bilateral short thumbs.

An index of thumb length was devised to allow mathematical comparison of short thumbs to the normal. The bone length of the proximal and the distal phalanges were taken from lateral radiographs and the length of the proximal phalanx was divided by the length of the distal phalanx. Considerable data on normal thumbs were available from previous studies

in Heberden's nodes. Of 200 normal thumbs in women the average thumb length index, hereafter called index was 1.38 ± 0.093 . There was no significant difference between right and left thumbs. Of 48 short thumbs of adult people the average index was 2.11 varying from 1.98 to 2.38.

The rate of growth was observed by means of repeated radiographic examinations made on 21 girls between the ages of 6 and 14 years. The observations on any one individual never extended over two and one half years. The epiphyses of the terminal phalanx in short thumbs were observed to close as early as 10 years in three thumbs and were found closed at 11 years in seven thumbs and 12 years in five thumbs. The epiphyses of the opposite normal thumb was closed in one instance at 11 years and was open in two instances at 11 and 12 years. The index of the short thumb was seen to increase in successive years from an average of 1.38 at 8 years, 1.84, 1.88, 2.02, 2.12, 2.10 and 2.14 at 14 years, while the index of the normal thumbs at the same ages was 1.44, 1.50, 1.41, 1.32, 1.51, 1.52 and 1.58. The numbers are small and measurement is never exact but the increasing disparity in the short thumbs to the normal thumb continues until growth stops. According to *Greulich* and *Pile* the epiphyses of the terminal phalanx of the thumb normally closes at thirteen and a half to fourteen years in girls.

Before investigating heredity the influence of maternal age and of birth order were determined. Among 84 people with short thumbs whose mother's age at time of birth was available the average maternal age for affected individuals was 28.08 years, compared to 27.5 years for their 205 sibs. There seemed to be no significant difference between the sexes. The Chi Square determination for the birth order was found to be 13.1323 for 6 degrees of freedom. This revealed the P was greater than 0.02 and less than 0.05 and was considered to be of no significance.

In analysing the mode of inheritance the study of pedigrees is of great importance. Actually 76 pedigrees of individuals with shorth thumbs have been assembled. These families include 328 sibs of whom 100 were affected, 228 were not affected, an incidence of 30 per cent. The sexes were evenly divided, 162 males and 166 females. Of the affected 31 were males, 56 were females, incidences of 19 and of 33.7 per cent, thus showing nearly two to one (1.8 to 1) ratio of affected females to males. Inspection of the pedigrees shows that a parent was involved in 24 of the 76 families. This parent was the father nine times, the mother fifteen times. Three generations were involved in direct descent twice. The skipping of a generation, involvement of a grandmother and a grandchild, sparing the parent, occurred twice. Two maternal uncles with an affected mother were found twice. One maternal

uncle and in another family two maternal aunts were reported affected, the mothers in both families were normal. Short thumbs are not sex linked because inheritance from father to son occurred five times; from mother to daughter eleven times.

Traits inherited as dominants may appear to be recessive if penetrance is incomplete. On the other hand a recessive trait is inherited with a 1 : 1 ratio exactly like a dominant if one parent is affected. With one parent involved inheritance as a dominant is suspected and one half the progeny is expected to be affected. One half of the progeny is affected under these circumstances in a dominant trait because one parent is heterozygous. The same is true in a recessive trait if one child is affected. Under these circumstances the affected parent is homozygous for the trait, the unaffected parent must be heterozygous and half the progeny will be homozygous affected and the other half heterozygous. Many families with an affected parent and all normal children are then to be expected.

Since the data did not immediately suggest either simple dominant or simple recessive inheritance it was submitted to statistical test to see which possibility test fitted the facts. The family data was first tested for simple recessivity because of the number of families without an affected parent, the number of affected parents without affected children and the small proportion of affected children. For this purpose the families were divided into those with an affected parent and those without an affected parent. When correction was made for small family size on the basis of a recessive and assuming 3 : 1 proportions of normal to affected, it was found that in 52 families there were 212 sibs of whom 58 were affected compared to 74 expected. The difference is 4.7 times the standard deviation of 4.9 and can hardly be explained on the basis of chance. The sexes were evenly divided among the sibs but 37 of the affected were women and only 11 were men. If a like number of men had been affected the affected number would have equalled the expected and penetrance would be complete. It seems obvious that in these families penetrance in women is complete, in men it is only 57 per cent.

In the families with one parent affected even in a recessive trait 1 : 1 ratio of normal to affected should be found because one parent in such a case is homozygous and the apparently normal parent is heterozygous. After correction for small family size it is found that in 23 families 36 are affected among 113 sibs compared to 58.8 expected. The difference of 21 is over four times the standard deviation and cannot be explained on a basis of chance. Here however the sexes are equally represented both in total sibs and affected sibs so the adjustment applied previously does not help.

Penetrance in this instance is 61 per cent. If the two groups are added together we have 114 of 325 sibs affected compared to 133 expected for penetrance of 86 per cent.

The entire group was then tested for simple dominance on a 1 : 1 basis assuming that the normal parents may have been affected but not recognized because of incomplete penetrance. In this instance of 325 sibs 94 were affected compared to 173 expected, a difference of nearly ten times the standard deviation. This is penetrance of 54 per cent. Here again men were affected only about two-thirds as frequently as women. Considered alone women showed only 64 per cent penetrance. This is the poorest fit yet. Pedigree analysis is not convincing but seems to indicate that the inheritance of short thumbs is best explained on the basis of a simple recessive with irregular penetrance.

An estimate of gene frequency can be made from the data at hand. The gene frequency obviously is the same for men as it is for women, the difference in incidence depending upon the lack of penetrance in men. The incidence in white women in the survey of the general population was found to be 0.66 per cent. Calculation shows that 0.66 per cent of the population is genotypically affected, 14.9 per cent are phenotypically normal but genotypically carriers and 84.4 per cent are completely normal.

One of the interesting surprises of this investigation has been the recognition of associated minor and non disabling defects of the bones of the hands and the feet. These defects have been found in subjects with short thumbs, they have been found in non affected relatives of subjects with short thumbs and they have been found in subjects not known to have affected relatives. These defects have been seen bilaterally as well as unilaterally. They include short terminal phalanx of the middle finger, short fourth metacarpal bone, short fifth metacarpal bone, short terminal phalanx of the great toe, short first metatarsal bone, short fourth metatarsal bone.

In 95 short thumbed individuals, short third terminal phalanges of the fingers were seen in four. In 9804 normal thumbed people seen in the survey it was seen once. A short fourth metacarpal bone was found once in 95 short thumbed individuals, never in the survey but was seen twice in other people. A short fifth metacarpal bone was seen twice with short thumbs, once in the survey and twice otherwise. A short terminal phalanx of the great toe was seen twice in short thumbed individuals, but not otherwise. A short metatarsal bone of the great toe was seen once in a short thumbed individual and not otherwise. A short fourth metatarsal bone was seen once in 95 short thumbed individuals, once in 818 people in the survey whose feet were examined and twice casually.

It seems safe to conclude that these anomalies are much rarer than short thumbs having been seen eleven times in 95 people with short thumbs and only eight times among 9838 people of the survey. They were found only four times in the survey without associated short thumbs. Six other instances were found on casual observation. The thumb is by far the most susceptible location and the terminal phalanx of the middle finger is next for these associated anomalies of the bones of the hands and feet.

Conclusion

Short thumbs occur throughout the human race as a non disabling anomaly in varying proportion depending upon sex and race. The highest incidence was seen in white women where it was found to be 0.66 per cent, compared to 0.17 per cent in white men. The deformity is confined to the terminal phalanx which is short at birth and it stops growing two years sooner than the normal. The anomaly seems to be inherited as a single autosomal factor recessive somewhat irregular with only about one fourth penetrance in males. This anomaly is associated frequently with other short bones of the hands and the feet.

Discussion

L. S. Wildervanck (Groningen): I have examined several families with short thumbs. The heredity was always *dominant*, so it is in most families described in the literature. The heredity of short terminal phalanges of the thumbs combined with brachyphalangy of other fingers, most of them *not* the terminal phalanx, and of brachyphalangy of *only* other fingers, is according to the literature nearly almost dominant too. Don't you find it remarkable that your families show a *recessive* mode of heredity?

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CONTRIBUTION TO THE STUDY OF THE INHERITANCE OF DYSOSTOSIS CLEIDOCRANIALIS

By G. A. WITKOP-OOSTENRIJK

Cleidocranial dysostosis is characterized by multiple defects of bone formation, most often in bones preformed in membrane, but also occurring in bones of chondral origin. Anomalies of muscles and joints may also occur, these being secondary to the skeletal defects. The clinical features vary widely but abnormalities of formation of the skull and clavicles, as suggested by the name, are the most frequent manifestations. Typically the skull is brachycephalic with decrease in the occipitofrontal diameter and increase in the transverse diameter; the cranial bosses are prominent and the sagittal suture is usually depressed. Abnormalities of the teeth are characteristic, the deciduous dentition is usually normal but the permanent teeth are very slow to erupt and many never appear. The palate is usually highly arched. The clavicular defects may vary from a small defect in one clavicle to complete absence of both clavicles. The patients show an unusual motility of the shoulder girdle. Associated defects in the central nervous system have been described by several authors, but these are apparently infrequent.

The condition causes very little disability in most affected persons, they usually live out a normal life span.

Four families have been studied, containing ten individuals exhibiting typical changes of cleido-cranial dysostosis. Of these patients pedigrees were composed going back as far and including the great-grandparents of the probands. No consanguinity has been found.

Family I. The proband was admitted to the department of stomatology because of a swelling of the lower jaw. The findings of cleido-cranial dysostosis were secondary. His head was typically large and brachy-

cephalic with persistence of the fontanelles and prominent cranial bosses. Bilateral aplasia of the distal two-thirds of the clavicles was noted. Films of the jaws revealed retention of twelve teeth.

A sister, normal on examination has a child, who goes to a school for mental defectives and who is suffering from kyphosis. One of the sisters of his mother has an epileptic child. The father's sibship is reported to be normal.

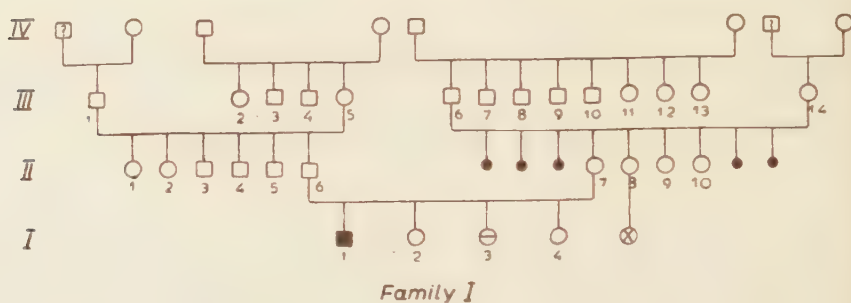


Fig. 1

Family II. The proband was admitted to the department of stomatology because of non-eruption of the permanent teeth. On radiological examination he presented typical changes of cleido-cranial dysostosis. In addition, he suffers from coxa vara. His sister is reported by her relatives and the attending physician to have symptoms of cleido-cranial dysostosis. The father of the proband has a rather square skull and an easily visible groove in the midline. The permanent teeth did not erupt. On radiologic examination the usual changes were noted. One of the father's sister was

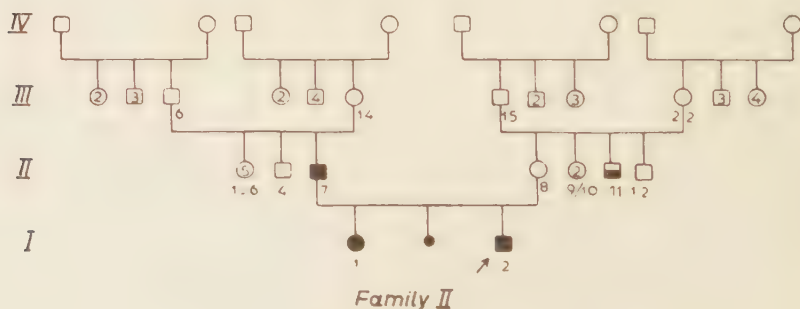
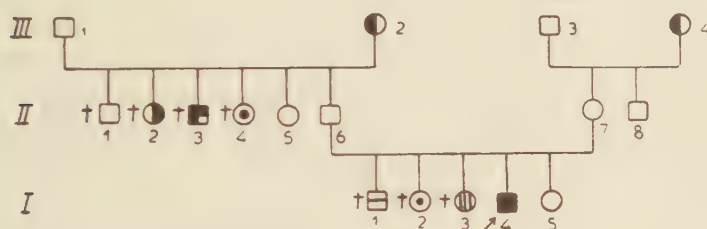


Fig. 2

mother of two little daughters, who died of convulsions, a third child suffered from a congenital vitium cordis. His mother's brother underwent an operation for a tumor cerebri.

Family III. The proband was admitted to the neurosurgical department because of a reticularsarcoma cerebri. The findings of cleido-cranial dysostosis were secondary and not related to the reason for hospital admission. His skull was brachycephalic with wide spacing of eyes and broad flat nose bridge. Bilateral aplasia of the distal two-thirds of the clavicle was noted. His deciduous dentition was delayed; only eight permanent teeth had appeared. A brother died of tuberculosis, a sister died of convulsions, a second sister of diphtheria. His two grandmothers suffer from diabetes mellitus.



Family III

Fig. 3

Family IV. The proband was admitted to the stomatologic department because of eruption of some of her permanent teeth, while she had been wearing dentures for some years. Her permanent teeth did not erupt till then. On physical and radiologic examination she presents the typical changes of cleido-cranial dysostosis. Her eldest sister lived only fifteen minutes, she is reported by her mother to have been abnormal just like the proband with a large skull, depressed nosebridge, wide fontanels and a short humerus. Her eldest brother died in the children's hospital because of dyspepsia. The pathography and the radiologic examination present the typical defects occurring in cleido-cranial dysostosis. A second sister is normal on physical examination, but suffers from an bronchial asthma and enuresis. The dentist found four non-erupted permanent teeth. The last born child died post partum. The mother reports, that this child also presented the same typical changes as the others, so it may be assumed, that this child also was suffering from cleido-cranial dysostosis. The mother

of the proband suffers from diabetes mellitus, a few years ago she underwent an operation for carcinoma mammae, she presents no typical changes of cleido-cranial dysostosis. One of her brothers has kypho-scoliosis and clubfeet. The father of the proband was admitted to the department of stomatology because of foetor ex ore. His skull is brachycephalic with prominent bosses and a marked furrow along the line of the sagittal suture, the eyes were wide apart with the bridge of the nose being depressed. He was able to bring the shoulders forward until they touched in the midline. Most of the permanent teeth are retained and erupted. A daughter of one of the father's brothers has an agenetic P_{2sd} : a sister of the father has two permanent teeth retained, her son has an agenetic P_{2ss} and an agenetic P_{2sd} .

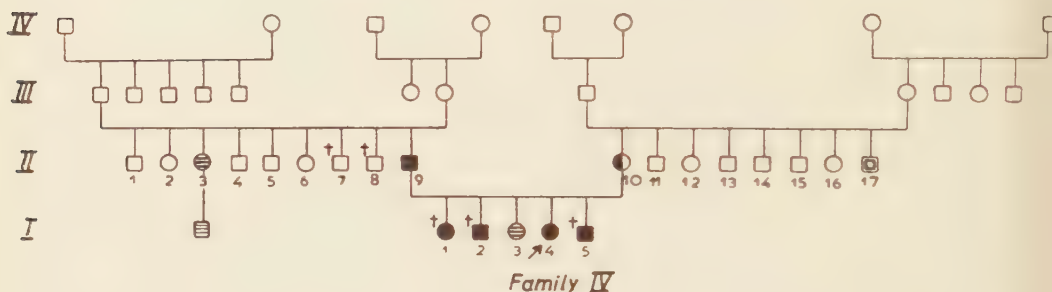


Fig. 4

In these families there are ten individuals with cleido-cranial dysostosis. Among our pedigrees there are two with multiple cases in two generations and two with isolated cases. Our pedigrees suggest the action of a dominant gene.

Descriptions of the disease are found in several languages. There seems to be general agreement in the literature, that the majority of cases is inherited as a Mendelian dominant.

In 1946 *Lasker* reviewed nearly all cases known in literature, he found:

- (1) the expected ratios for a Mendelian dominant closely approximated,
- (2) there was no significant difference in the incidence in males and females,
- (3) sex linkage seemed not to be involved,
- (4) the found ratio for sibships differs widely from the ratios usually encountered in diseases due to recessive genes. Only one consanguineous mating was met with and there was a transmission of a dominant type (*Villaret and Francoz*).

Lasker concludes that the majority of cases of cleido-cranial dysostosis are inherited as a Mendelian dominant with high penetrance. He suggests that it is quite possible, that all cases may be explained in that way if the responsible gene occurs frequently as a mutant.

In 1951 *Herndon* published a family containing three individuals exhibiting typical changes of cleido-cranial dysostosis. Accepting the hypothesis that most cases show evidence of the action of a dominant gene with high penetrance and that a smaller proportion of cases occur sporadically, he considers three possible situations that would fit these facts. These are:

- (1) there are two etiologically distinct types, one hereditary type and one environmental, the c. f. phenocopies of *Goldschmidt*,
- (2) there are two separate mutations, the majority of cases representing the heterozygous state of a dominant mutation and the apparently sporadic cases representing the homozygous state of a recessive mutation producing a nearly similar biologic effect,
- (3) the sporadic cases represent the appearance of new mutations.

The available data are according to *Herndon*, most compatible with the third alternative. He suggests, that mating selection may be operating with sufficient effectiveness to reduce the number of mutant genes by nearly 50% in each generation.

It seems reasonable to conclude that our findings agree with the data of the literature.

As regards the affections found in the relatives of the patients as: reticulosarcoma, convulsions, meningitis, clubfoot, diabetes mellitus etc. we remark that these complaints likewise are found by *Stocks*, *Carpentier*, *Roussy*, *Burkens*, *La Chapelle* and *Groen*, *Kilgore* and *Lasker*. These associations are considered by the authors as probably coincidental. We cannot subscribe that conception for we suggest that the described affections have a higher incidence in the relatives of the patients than in the general population. These findings can perhaps be considered supporting the theories of *Sillevis Smitt* concerning the stigmata degenerationis.

It would take us too far afield, to enlarge on this subject here.

The non-eruption of teeth found in otherwise healthy relatives of the patients may be considered as "formes frustes" of the cleido-cranial dysostosis.

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ETIOLOGICAL FACTORS IN CLEFTS OF THE PALATE AND LIP

By F. C. FRASER

The bulk of this paper has recently been published in an article entitled "Thoughts on the etiology of clefts of the palate and lip" which appeared in *Acta Genetica et Statistica Medica* 5, 358-369, 1955. In addition, the following information is presented:

(1) The difference in maternal weight at conception between mothers giving birth to a child with cleft lip and palate and control mothers, which was previously said to be statistically significant, has become non-significant upon collection of further data.

(2) The risk that the sibling of a child with a cleft of the lip and/or palate will be similarly affected does not appear to be any higher when the parents are consanguineous than when they are not.

(3) The risk that the sibling of a child with a cleft of the lip (with or without cleft palate) will be similarly affected does not appear to be higher when there is an affected relative than when there is not. A similar conclusion is reached (though with less confidence, because of the smaller numbers involved) for siblings of a child with cleft palate alone.

(4) A search for prenatal etiological factors proved relatively fruitless. No significant differences between the families of children with clefts of the lip and/or palate and control families were found with respect to maternal or paternal age; birth rank of propositus; frequency of abortions and miscarriages; time from birth of child born previous to the propositus (or if the propositus was the first-born, time from marriage); history of maternal menstrual irregularity; history of bleeding, febrile illness and attempted abortions in the first trimester. There were no instances of the mother undergoing an operation or a high altitude aeroplane flight during

pregnancy in the cleft lip and/or palate group. However there was some suggestion that the mothers of children with cleft lip and/or cleft palate had a higher frequency of reproductive tract pathology such as uterine fibroids, prolapsus uteri, and ovarian cysts, than did the control mothers. The significance of this remains to be evaluated after further data are collected.

Discussion

P. Fogh-Andersen (Copenhagen): Calls attention to the typical sex-distribution in man: cleft lip with or without cleft palate most often in males, cleft palate alone more frequent in females.

Mentions 3 Danish families with both parents affected in the apparently rare combination one parent cleft lip and cleft palate, the other cleft palate alone (publ. in *Opera Ex Domo Biol. Hered. Hum. Univers. Hafn.* Vol. 4, 230, 1942). In the two cases the parents got perfectly normal children (4 and 1); in the third case the result was a child with cleft palate alone. These 3 cases do not in themselves allow of far-reaching conclusions, but they are in full accordance with the theories (1) that cleft lip with or without cleft palate is genetically different from cleft palate alone, and (2) that cleft lip with or without cleft palate is mostly of a recessive character and cleft palate alone dominant.

HEREDITARY DEFECTS OF DENTAL STRUCTURE

Schulze, C.: Acta genet. 7, 231-235, 1957

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ERBBEDINGTE STRUKTURANOMALIEN MENSCHLICHER ZÄHNE

Von C. SCHULZE

Neben den häufigen, überwiegend umweltbedingten rachitischen Hypoplasien der Zähne gibt es seltenere erbliche Strukturanomalien. Sie betreffen entweder den Schmelz oder das Dentin der Zähne und nicht, wie rachitische Hypoplasien, Schmelz und Dentin.

1. Die *erbliche Schmelzhypoplasie* wurde bisher meistens «angeborene Schmelzhypoplasie» oder «Amelogenesis imperfecta» genannt. Ihre Erbbedingtheit ist in den meisten Fällen erkannt worden. Eine genauere Kenntnis darüber, ob es verschiedene Arten erblicher Schmelzhypoplasien gebe und wie sie sich klinisch, histologisch und erblich unterscheiden, fehlte bisher.

Ich habe 6 Sippen erforscht, in denen sich die Anomalie unvollständig dominant x-chromosomal vererbt. In allen 6 Sippen wird die Anomalie von behafteten Männern auf alle Töchter, nie aber auf einen Sohn vererbt: bei den 18 behafteten Männern mit Kindern sind alle 27 Söhne frei von der Anomalie, alle 29 Töchter behaftet. Behaftete Frauen übertragen die Anomalie auf Söhne und Töchter, jedoch nicht auf alle. Insgesamt hatten 33 behaftete Frauen 44 Söhne und 43 Töchter; von den 44 Söhnen sind 22 behaftet, 22 nicht behaftet. Von den 43 Töchtern sind 30 behaftet, 13 nicht behaftet. Bei 12 Kindern bekam ich keine genügenden Auskünfte darüber, welchen Geschlechts sie waren und ob sie die Anomalie hatten oder nicht.

Die charakteristischen Unterschiede in der Übertragung der Anomalie durch Männer und Frauen beweist, daß dominanter x-chromosomaler Erbgang vorliegt. Auch das Verhältnis behafteter Männer zu behafteten Frauen, das 25 zu 61 beträgt, spricht dafür. Denn da Frauen zwei X-Chromosome haben, Männer aber nur eines, sind bei dominant x-chromo-

somalen Anomalien im Durchschnitt doppelt soviel behaftete Frauen wie Männer zu erwarten.

Der klinische, röntgenologische und histologische Befund der Zähne weist in allen 6 Sippen gleichförmige Unterschiede zwischen den Geschlechtern auf: Die Zähne der Männer sind dunkelgelb, manchmal rotgelb. Die Oberfläche ist glatt und hart. Die Zahnform weicht von der normaler Zähne ab: es fehlen die charakteristischen Wölbungen der Seitenflächen, die Zähne sind kleiner als üblich. Dadurch entstehen Lücken zwischen den einzelnen Zähnen.

Die Ursache dieser Formabweichungen zeigen die Röntgenaufnahmen: überall fehlt der intensive Schatten, den der Schmelz normaler Zähne wirft.

Klinisch-röntgenologisch könnte man also von Schmelzaplasie sprechen. Die histologischen Bilder dagegen zeigen eine dünne, atypische Schmelzschicht. Prismen und interprismatische Substanz, Retziusstreifen, Para- und Diazonien und die übrigen typischen Struktureigentümlichkeiten fehlen. Nur die einfachen Fortsätze der Dentinkanälchen in der untersten Schmelzschicht sind vorhanden. Statt der normalen Elemente sind gelegentlich, besonders an den Kronenseitenflächen, atypische fadenartige zu erkennen.

Die Zähne behafteter Frauen sind nicht so intensiv gelb wie die der Männer, zeigen aber eigentümliche Riefen und Rillen im Schmelz. Diese Rillen sind, im Gegensatz zu den horizontal verlaufenden Rillen rachitischer Zähne, immer vertikal angeordnet. Der Schmelz ist so dünn, daß an den Schneidekanten Schmelzgrate abzubrechen pflegen, wodurch atypische Zahnkonturen entstehen. Milch- und bleibende Zähne sind gleich betroffen.

Der hypoplastische Schmelz äußert sich im Röntgenbild dadurch, daß nur da ein intensiver Schatten geworfen wird, wo Schmelzteile seitlich getroffen oder wo Höcker zur Deckung gebracht worden sind. Zahnwurzeln und Alveolarfortsatz sind bei den Frauen wie bei den Männern normal.

Histologisch fällt bei den Frauen die unterschiedliche Dicke der Schmelzschicht ins Auge. Die normalen Struktureigentümlichkeiten sind zwar vorhanden, aber atypisch angeordnet und durchsetzt mit Farb- und Luft einschüssen.

Diese Unterschiede im Schweregrad der Anomalie bei Männern und Frauen sind dadurch bedingt, daß das normale Allel in dem zweiten X-Chromosomen der Frau das kranke an seiner vollen Äußerung hindert, während sich bei den Männern das kranke Gen voll auswirkt, weil ihm ein Allel fehlt. Das pathogene Gen ist deshalb unvollständig dominant.

Auf kleine Unterschiede im Manifestationsgrad der Anomalie bei Frauen kann ich nicht eingehen. Wohl aber möchte ich auf einen bedeutsamen Unterschied zwischen Behafteten der Sippe 1 und Behafteten der Sippen 2, 3 und 4 hinweisen, der die Bißform vor allem der Männer betrifft. Die Sippen 5 und 6 müssen in diesem Zusammenhang unberücksichtigt bleiben, weil sich die Bißform der Männer nicht mehr sicher feststellen ließ.

In Sippe 1 haben die behafteten Männer Deckbiß oder normalen Biß; in den Sippen 2–4 haben die Männer dagegen offenen Biß, teilweise in einer ganz ausgeprägten Form. Wie ich durch histologische Untersuchungen mit Sicherheit feststellen konnte, handelt es sich nicht um einen rachitisch offenen Biß; natürlich auch nicht um einen durch Lutschen entstandenen, sondern um eine bisher nicht bekannte Form. Dieser offene Biß kommt nie ohne gleichzeitige Schmelzhypoplasie vor; bei Frauen war er, wenn überhaupt, nur angedeutet. Es ist anzunehmen, daß die Korrelation zwischen Schmelzhypoplasie und offenem Biß auf pleiotroper (polyphäner) Wirkung eines und desselben Gens beruht. Es ist weiter anzunehmen, daß der Unterschied in der Bißform zwischen Behafteten der Sippe 1 und Behafteten der Sippen 2 bis 4 durch zwei spezifisch verschiedene Gene bedingt ist. Die beiden Gene gehören vermutlich der gleichen Allelenreihe an. Übrigens war auch histologisch ein Unterschied zwischen den in Rede stehenden Sippen vorhanden: in Sippe 1 ließen sich bei behafteten Männern an der Schmelz-Dentingrenze gelegentlich ganz kurze Prismenstücke erkennen, in den anderen drei Sippen fehlten sie immer.

Eine dritte Art von Schmelzhypoplasie vererbt sich autosomal regelmäßig dominant. Klinisch stehen im jugendlichen Gebiß vor allem Verfärbungen der Zähne im Vordergrund: sie brechen entweder schon gelbrot durch oder verfärben sich bald nach dem Durchbruch. Kreidige, gelbliche und rötliche Flecken treten auf, wobei der Glanz der Schmelzoberfläche verloren geht. Sehr bald bilden sich Defekte im Schmelz: sie beginnen an den Schneidekanten oder Höckerspitzen und schreiten langsam zum Zahnhals fort. Im älteren Gebiß stehen dann die Defekte im Vordergrund. Diese Symptome variieren bei den einzelnen Angehörigen der Sippe beträchtlich. Eine Vorstellung darüber, wie die Defekte des Schmelzes auf der Höckerspitze beginnen und dann zervikal fortschreiten, vermittelt das Gipsmodell des Probanden: je nach der Länge der Zeit, die die Zähne schon funktionieren, sind die Defekte verschieden groß.

Die Ursache dieser Zerstörungen offenbaren Röntgenbefund und histologischer Befund. Im Röntgenbild erkennt man, daß die Mineralisation des Schmelzes so gering ist, daß sie sich von der des Dentins kaum unterscheidet. Gleichzeitig sieht man, daß noch im Knochen liegende oder noch von

Schleimhaut bedeckte Kronenteile unveränderte Konturen haben, daß also erst nach dem Zahndurchbruch Defekte auftreten.

Die mangelhafte Mineralisation des Schmelzes äußert sich histologisch an einer deutlichen Querstreifung der Prismen, die wir sonst nur in der Zone der Demineralisation bei der Karies finden. Daneben findet sich in manchen Bezirken eine im ungefärbten Schliff goldgelbe Körnung der Prismen und eine Verbreiterung der interprismatischen Substanz. Die entscheidende Störung bei dieser Art von Schmelzhypoplasie ist also in einer unzureichenden Mineralisation des Schmelzes auf dem Boden einer erbbedingten Schwäche der Ameloblasten zu suchen.

Ganz ähnlich sind die Anomalien des Schmelzes bei den behafteten Angehörigen zweier weiterer Sippen. Vermutlich ist der Erbgang rezessiv, möglicherweise auch unregelmäßig dominant. Es kann hier nicht näher auf diese Art der erblichen Schmelzhypoplasie eingegangen werden.*

2. Genauer erforscht als die verschiedenen Arten erblicher Schmelzhypoplasie (es gibt außer den vier von mir erforschten mindestens zwei weitere Arten, wie sich aus der Literatur ergibt) ist die *erbliche Dentinhypoplasie*, die bisher meistens opaleszierendes Dentin oder Dentinogenesis imperfecta genannt worden ist. Sie vererbt sich immer autosomal und regelmäßig dominant. Nur Lyons hat in seiner Sippe dominant x-chromosomal Erbgang vermutet. Wahrscheinlich handelt es sich aber um zufällige Verteilung oder um fehlerhafte Angaben in der Anamnese.

Ich selber habe zwei Sippen erforscht. In beiden Fällen handelt es sich um autosomalen, regelmäßig dominanten Erbgang.

Gleichartig ist in beiden Sippen die äußere Form der Kronen und Wurzeln: die Zahnkronen sind kürzer als normal und in Zahnhalshöhe stark eingezogen; dadurch erscheinen püzarartige Formen. Die Farbe ist graubraun, der Schmelz schimmert bläulich und der ganze Zahn hat eine an Bernstein erinnernde Transparenz. Alle Zähne sind thermischen und chemischen Reizen gegenüber völlig unempfindlich. Unterschiede bestehen in beiden Sippen in bezug auf die mechanische Widerstandskraft. In Sippe 1 treten gehäuft Frakturen äußerlich intakter Zähne zum Beispiel beim Kauakt auf; in Sippe 2 kommen solche Frakturen nicht vor, dafür springt der Schmelz in relativ großen Stücken vom Dentin ab, was in Sippe 1 höchstens angedeutet in Erscheinung tritt.

Im Röntgenbild fällt in beiden Sippen die geringe Röntgendichte der Zähne, vor allem der Zahnwurzeln auf. Auch die völlige Obliteration der

* Genaue Angaben und Bilder in: Chr. Schulze: «Erbbedingte Strukturanomalien menschlicher Zähne». Urban u. Schwarzenberg, München/Berlin 1956.

Pulpencava ist in beiden Sippen vorhanden. Sie tritt schon während der Wurzelbildung in der Kronenpulpa auf und hat bei Abschluß der Wurzelbildung auch die Wurzelpulpa schon so eingeengt, daß sie nur als schmaler Strich noch sichtbar ist. Nur in Sippe 2 treten dagegen große periapikale Ostitiden auf, die sich merkwürdigerweise auch an völlig intakten Zähnen bilden. Ich vermute, daß die zugrundeliegende Nekrose der Pulpa durch überstürzten Anbau von Dentin bzw. dabei auftretende giftige Stoffwechselprodukte zustande kommt.

Histologisch lassen sich in Schmelz und Dentin Unterschiede in den beiden Sippen feststellen. In beiden Sippen ist der Schmelz etwa normal dick und zeigt deutliche Retziusstreifen als Ausdruck rhythmischer Mineralisationsvorgänge; daneben kommen auch gewisse Mineralisationsmängel vor. Stärker vergrößert verhält sich die Schmelzdentingrenze in beiden Sippen aber unterschiedlich. In Sippe 1 haben wir eine glatte Grenze, in Sippe 2 die gewohnte wellenförmige.

Im Dentin fehlen praktisch normale Dentinkanälchen. Statt dessen gibt es astartig verzweigte, ganz dünne Kanälchen, die allerdings auch bei starker Vergrößerung kein Lumen erkennen lassen. In beiden Sippen finden sich lediglich in den Höcker-spitzen Bündel normaler Dentinkanälchen, die in Sippe 1 aber viel strenger angeordnet sind als in Sippe 2. Noch deutlicher unterscheidet sich das Dentin in beiden Sippen dadurch, daß in Sippe 1 peripher niemals normale Dentinkanälchen vorkommen, während in Sippe 2 zunächst eine ganz dünne Schicht normalen Dentins gebildet worden ist.

Ob die Unterschiede in den beiden Sippen durch spezifisch verschiedene Gene zustande kommen oder durch Nebengene, wage ich einstweilen nicht zu entscheiden. Da entsprechende Unterschiede zwischen den Sippen auch sonst beschrieben worden sind, halte ich sie jedenfalls für genisch bedingt. Ich erforsche gerade eine dritte Sippe mit erblicher Dentinhypoplasie und hoffe, daß sie zur Klärung beitragen wird.

Auf die von anderer Seite vermutete Beziehung der erblichen Dentinhypoplasie zur Osteogenesis imperfecta kann ich nicht mehr eingehen; ich glaube nicht, daß diese beiden erblichen Hypoplasien wesensgleich sind. Auch auf die Bedeutung, die die Erforschung dieser Anomalien im Hinblick auf das strittige Problem der wechselseitigen Beziehungen von Schmelzorgan und Zahnpapille bei der Histogenese von Schmelz und Dentin hat, kann ich hier nur noch hinweisen.

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HEREDITARY DEFECTS IN ENAMEL AND DENTIN

By C. J. WITKOP

A survey of 64,000 children was made in the State of Michigan for hereditary defects of enamel and dentin. The purpose of this study was to establish the prevalence of these conditions in the general population; to classify the various types of hereditary defects of enamel and dentin; to determine their modes of inheritance; to conduct linkage studies where possible, and to study the histological and histochemical factors present in the defective teeth.

Methods

The population surveyed consisted of children from Muskegon and Grand Rapids examined during the city water flouridation program and children from 42 counties seen during a topical flouride program. Each suspected case was referred to this investigator, who interviewed each family, made a diagnosis, and obtained a pedigree for each case believed to be genetically determined. Following this, every living member of the kindred was examined, provided he lived in the State of Michigan. At this time blood and saliva samples were obtained and a PTC taste test given. Extracted and exfoliated teeth were obtained for histological studies and intra-oral roentgenograms were taken where indicated. Selected patients were brought to the clinical center, National Institutes of Health, Bethesda, Maryland for detailed clinical investigations and restorative procedures.

Findings

All enamel defects, loosely classified as amelogenesis imperfecta, occurred once in 12,000 to 14,000 persons in the general population. Amelogenesis imperfecta includes at least 5 distinct clinical and genetic entities. In the first 4 of these all the teeth are affected.

1. Hypoplasia of enamel

In this condition the enamel is thin. It is only about one-fourth the thickness of normal enamel, so that the teeth appear to be small. The surface texture is granular and rough. This enamel is very hard. Root and dentin formation appear to be normal. This condition may be transmitted as an autosomal dominant trait.

2. Hypocalcification

In this condition the enamel is dull brown on both the erupted and unerupted teeth. The enamel is rough, softer than normal, and can be penetrated for some distance by a dental explorer. Some degree of hypoplasia exists in this condition as the full thickness of enamel is not formed on the occlusal one-half of the crown. This condition is transmitted as an autosomal dominant trait, although some pedigrees show a predominance of affected females.

3. Hypomaturation

In this condition the enamel is an opaque white. The enamel is soft and can be penetrated by an explorer, but the surface is usually smooth except in areas where it is easily abraded by occlusal contacts or a tooth brush. The enamel appears to be of normal thickness on unerupted teeth. This condition is transmitted as an X-chromosomal recessive trait.

4. Pigmented Hypomaturation

This condition is also known as hereditary brown teeth. The enamel appears to be nearly normal in thickness and surface consistency, but with a brown pigment extending throughout the full thickness of the enamel. The enamel is not as hard as normal enamel, and it tends to chip from surfaces in occlusion. We do not have sufficient data to determine the mode of inheritance in this condition, but it is probably inherited as an autosomal dominant trait.

5. Local hypoplasia

This is the only hereditary enamel defect we have seen that does not always affect the complete dentition. The teeth show brown hypoplasia usually limited to the buccal aspect of the crown. Usually both the primary and secondary dentitions are involved, but occasionally only the primary

dentition shows the defect. This condition is transmitted as an autosomal dominant with incomplete penetrance.

Two distinct dentin defects were found.

1. Dentinogenesis imperfecta (Capdepon's teeth or opalescent dentin).

In this condition the teeth vary from opalescent blue to amber brown in color. The enamel readily splinters from the dentin, when subjected to occlusal stresses. Over 300 people have been examined with this condition. It is transmitted as an autosomal dominant trait. No case that could represent a mutation was found. Ten *propositi* were found during the survey. This condition occurred once in 6000 to 8000 children in the general population.

The probability of transmission of this condition determined from the probands in the study was .50. Of the 110 sibships for which we have complete knowledge there were 171 affected individuals and 186 unaffected individuals when the probands, the one child sibships and the transmitters in each generation were eliminated. Some distortion in the sex distribution was noted, but it is the distribution expected nine times in one hundred by chance, so we concluded that this is within the expected distribution for an autosomally transmitted trait.

Variations in the manifestation of this trait are "shell" teeth similar to those described by *Rushton* in England, teeth containing normal sized pulp chambers, as well as those with the characteristic solid appearance.

Linkage data analyzed by the paired-sib method indicated no linkage with the secretor factor, but a possible linkage with PTC taste test where the probability for the X^2 test is less than .001.

The homozygous condition for this trait was not seen. However, in two matings both parents were heterozygous for this trait. One mating produced seven pregnancies with only two viable offspring. These children were both affected, but appeared to be heterozygous for the condition. The other five pregnancies resulted in miscarriages between the fourth and fifth months of gestation. These may represent a lethal effect of the homozygous condition.

2. Rootless teeth or dentin dysplasia.

Only one case of this condition was found during the survey. The crowns of the teeth appear normal. The teeth however are malaligned resembling the wandering teeth seen in the late stages of periodontitis. The roots of the teeth are distorted, blunted, or absent. Pulp chambers and root canals are frequently absent in these teeth. This condition is transmitted as an autosomal dominant trait.

Discussion

P. O. Pedersen (Copenhagen): Have any cases with disturbances in enamel and dentine formation of the types described been found without a demonstrable hereditary background?

C. J. Witkop (Bethesda, Md.): Yes, we found many cases in our survey which resembled the conditions described here but in which we could show no hereditary factor in their formation. One helpful criterion for distinguishing initially between hereditary or non-hereditary types of defect is that hereditary defects usually affect all the teeth while the non-hereditary types usually affect individual teeth or groups of teeth, as in fluorosis. Of course, some could be rare recessives which would be difficult to determine.

P. O. Pedersen: Referring to the rather striking sex differences in the distribution of different types of amelogenesis imperfecta just reported by Dr. *Schulze* I wondered why Dr. *Witkop* did not come across similar differences and whether he felt that the pattern of disturbances described by Dr. *Schulze* would fit into that of his own five entities?

C. J. Witkop: Dr. *Schulze* is talking about enamel hypoplasia. I have only two small pedigrees. The mutations involved here may not be the same. I do not want to give the impression that these are all of the hereditary defects in enamel and dentine. These are all I have found to date. I believe that Dr. *Schulze* has shown very nicely the sex-linked dominance of enamel hypoplasia. I had suggested this at the last American meeting but, as the pedigrees were small, I hesitated in making this interpretation. I am very glad to see the large pedigrees presented by Dr. *Schulze*.

P. O. Pedersen: It has been stated in literature that in dentinogenesis imperfecta (with or without osteogenesis imperfecta) the enamel formation is normal. Dr. *Schulze* showed a case in which it was not. In view of the early heavy attrition of the enamel in many cases of dentinogenesis imperfecta, and in the light of their histological experience, were the two speakers of the opinion that enamel formation was generally normal in dentinogenesis imperfecta?

C. J. Witkop: No it is not always normal. I think one of the important things to decide is whether the primary genetic defect is in the dentine or in both dentine and enamel, as here we would have both ectodermal and mesodermal structures involved if the latter were true. I feel that the primary genetic defect is on the dentine formation and the enamel defects, when they occur, are secondary.

INHERITANCE OF DEAF MUTISM

Pfändler, U.: Acta genet. 7, 241-244, 1957

La Chaux-de-Fonds, Suisse

UNE FORME SEMILÉTALE DE LA SURDIMUTITÉ RÉCESSIVE

Par U. PFÄNDLER

La surdimutité est une infirmité fréquente. La proportion générale des sourds-muets dans différents pays d'Europe et d'Outre-mer est estimée environ à $0,5\text{‰}$. — Mais en Suisse, cette fréquence est plus grande, puisqu'elle s'élève à 2‰ , et que 50 à 70 % de ces malades sont atteints de la *surdimutité récessive*.

Nous savons que la surdimutité récessive est plus fréquente dans certains isolats. Des mutations se sont produites dans différentes régions du pays, mais par suite des variations du taux de consanguinité, et pour d'autres raisons encore, il y a davantage de sourds-muets récessifs dans certains groupes de population. C'est le cas tout particulièrement pour quelques régions de la Suisse.

Avec l'appui de l'Académie Suisse des Sciences Médicales, j'ai examiné à ce sujet, une région bien circonscrite de la Suisse orientale, le Werdenberg qui groupe actuellement environ 18 000 habitants. J'y ai dénombré 105 sourds-muets récessifs aujourd'hui vivants. La fréquence de cette tare s'élève par conséquent à $5,8\text{‰}$. — Elle est 5 fois plus élevée que dans la population suisse en général.

Les sourds-muets vivants, une partie de ceux qui sont décédés au cours des trois derniers siècles, ainsi que leurs frères et sœurs, leurs parents et leur parenté plus éloignée, ont été enregistrés dans 5 tableaux généalogiques. Ce ne sont pas des souches, puisque les sourds-muets ne remontent pas nécessairement à un couple ancestral qui leur est commun. Il s'agit d'une étude démographique détaillée. J'ai enregistré systématiquement tous les sourds-muets du Werdenberg, et je les ai groupés dans ces tableaux généalogiques, en recherchant les liens de consanguinité qui les unissent entre eux.

La plupart des sourds-muets vivants, ainsi qu'une partie de leurs frères et sœurs et parents, ont été examinés audiométriquement. Il s'agit sans aucun doute d'une forme à hérédité récessive. Les parents et ancêtres de sourds-muets sont généralement sains. La fréquence de la consanguinité chez les parents des tarés, s'élève à 15,3 %, c'est-à-dire qu'elle est 15 fois plus élevée que dans la population en général.

Les variations d'expressivité ne sont par négligeables. De nombreux sourds-muets présentent des restes d'ouïe, soit d'un, soit des deux côtés. Sur 172 éléments atteints, 152 sont sourds et muets, et 20 seulement. c'est-à-dire le 11,6 % d'entre-eux, sont sourds sans être muets.

Nous savons que le gène de la surdimutité récessive déploie un effet polyphénique. Cette tare s'associe fréquemment à d'autres anomalies. Les sourds-muets sont assez souvent faibles d'esprit, ils ont un palais ogival, et ils sont volontiers frappés d'infantilisme sexuel, d'hypogénitalisme. Les sourds-muets du Werdenberg ne se marient pratiquement pas, et lorsqu'ils se marient, ils n'ont que peu ou pas d'enfants. Il est à prévoir que la fréquence des mariages consanguins diminuera notablement au cours des prochaines décennies, et que de ce fait la maladie deviendra plus rare.

Nous en arrivons maintenant au point crucial du problème. Puisqu'il s'agit d'une hérédité récessive, nous devrions obtenir dans l'ensemble des fratries atteintes, 25 % de tarés et 75 % de frères et sœurs sains. Or ce critère ne se confirme absolument pas chez les sourds-muets du Werdenberg.

Sur 844 éléments de fratries atteintes, j'ai trouvé 172 sourds-muets. Mais il faut tenir compte du fait que les fratries saines dont les deux parents sont hétérozygotes, n'ont pas été enregistrées. Si nous appliquons différentes méthodes statistiques correctrices, et en particulier la méthode des germains de *Weinberg*, il ne nous reste effectivement plus que 68 sourds-muets sur 887 frères et sœurs. Cela représente 7,66 %, soit environ 8 % de tarés au lieu de 25 %.

Nous sommes en présence d'un énorme déficit de sourds-muets. Comment l'expliquer ? — Il ne peut pas être dû à la pénétrance incomplète du gène, cette dernière étant pratiquement totale pour la surdimutité récessive.

Frères et Sœurs sains		Sourds-muets		Décédés en bas-âge	
□	○	■	●	□	○
+	+	+	+	+	+
268	265	101	71	85	54
533		172		139	
844					

En examinant les fratries atteintes, nous sommes frappés par le fort pourcentage d'éléments décédés en bas-âge jusqu'à leur septième année y compris, mais surtout au cours de la première année de leur existence (139 sur 844).

Si nous prenons uniquement les enfants décédés en bas-âge au cours de la période 1876-1950, nous en obtenons 77 sur 569 frères et sœurs, soit 13,53 %. — Or les statistiques fédérales suisses pour la même période, nous donnent une mortalité moyenne de 13,2 % jusqu'à l'âge de sept ans. Notre observation est par conséquent conforme aux prévisions statistiques.

Voyons maintenant quelle est la proportion des sexes chez les sujets sains, les sourds-muets et les morts en bas-âge. Sur 533 normaux, 268 sont des mâles, et 265 des femelles. Nous avons donc une proportion sensiblement égale de frères et de sœurs sains. Nous trouvons par contre moins de sœurs que de frères sourds-muets (71 : 101), et moins de sœurs décédées en bas-âge, que de frères de la même catégorie (54 : 85).

Pour la période 1876-1950, nous comptons 53 frères et 24 sœurs décédés en bas-âge, soit un total de 77. — Or les statistiques fédérales correspondantes donnent respectivement 58,22 % de frères et 41,78 % de sœurs. En ramenant cette proportion à 77, nous obtenons 44,83 frères et 32,17 sœurs.

Comparons les valeurs du Werdenberg aux prévisions statistiques :

Observation :	53	24	77
Théorie :	44,83	32,17	77

Le $\chi^2 = 3,564$, c'est-à-dire qu'il n'est pas significatif. La proportion des frères et sœurs décédés en bas-âge dans les fratries de sourds-muets du Werdenberg, est encore conforme aux prévisions statistiques.

Les 25-8 = 17 % de tarés qui manquent, sont donc inexistants. Nous pouvons admettre que ces derniers étaient en réalité des homozygotes tarés non viables. Le gène de la maladie aurait éliminé 17 % de zygotes.

Nous sommes ici, sans doute, en présence d'une *forme semilétale de la surdimutité*. J'appelle semilétal, un facteur qui tue plus de la moitié des sujets avant l'âge de leur reproduction. Le gène pathologique responsable de cette tare dans le Werdenberg, éliminerait environ les deux tiers des embryons qui le renferment à l'état homozygote. Voilà sans doute la raison pour laquelle l'on a si souvent parlé de surdimutité sporadique.

Ce travail paraîtra in extenso dans le *Bulletin de l'Académie Suisse des Sciences Médicales*, 1957.

Discussion

S. Rayner (Lund): Only a short question to Dr. *Pfändler*.

If you deal with a sublethal gene, you often may find a higher frequency of abortion and stillbirth of the mothers.

I did not hear, if you mentioned anything about that in your paper.

Wildervanck, L. S.: Acta genet. 7, 244-248, 1957

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CONSANGUINITY AND CONGENITAL DEAF MUTISM IN THE NETHERLANDS. ARE THE PARENTS OF DEAF CHILDREN DETECTABLE AS HETEROZYGOTES?

By L. S. WILDERVANCK

Among 139 marriages which furnished the Institute with 187 deaf born children ("rubella children" etc. excluded) the parents were related to each other in 17 (i.e. 12.2%). They had 85 children of whom 28 were deaf. In 13 matings the parents were full cousins and if we take into account only those marriages, the proportion is 9.4%, with a standard deviation of 2.5%. In the whole population of Holland the proportion of consanguineous marriages is about 0.16% (*Polman*).

We may expect that most children congenitally deaf without obvious external cause, are suffering from the recessive type of deafness. Now it would be of great importance, both scientifically as well as practically, and this in the first place (genetic counselling!) if apparently normally hearing individuals who might be heterozygous for deafness, could be detected as carriers of the recessive gene. As heterozygotes for deafness,

and thus suitable to my purpose, we may first consider related parents with one or more deaf children, secondly not related parents having more than one deaf child, and thirdly parents having one (ore more) deaf children while there are more deaf relatives in the family.

There have been already some investigators who tried to solve this problem audiometrically (*Tinkle, Sécretan, Lindenor, Stevenson and Cheeseman, Johnsen*). They came to the conclusion that there are no typical aberrations in the audiograms of the parents of deaf children, or normally hearing children with one deaf parent, which may distinguish them as heterozygotes. As I was not fully satisfied by those investigations, I once more studied the problem on a set of parents, giving full details about the audiograms and pedigrees. The audiometrical examinations were performed with a Pedersen audiometer which can be regulated continuously from 125 Hz till 16.000 Hz in one decibel steps of intensity, by Professor H. C. Huizing, Audiological Department of the Ear-Nose Throat Clinic of the University.

The following audiograms with pedigrees are the result of my investigation.

I. Consanguineous marriages

No. 1. Five deaf children. Parents normal audiogram and also in one of the two normally hearing sisters. It is conspicuous how little difference there is between the five audiograms of the deaf siblings. In connection with this feature I will mention the investigation of *Ciocco, Hughson and Palmer*, on pupils of the Pennsylvania School for the Deaf, who found a significantly lesser difference between the auditory acuity of deaf siblings than of not related deaf mute children.

No. 2. One deaf child. Parents normal.

No. 3. One deaf child. Father: on both sides a dip at 4000 Hz, in the right ear till 60 db, in the left ear till 40 db. This dip may be traumatic (noise). Mother normal.

No. 4. One deaf child. A sister suffered from amaurotic idiocy, two cousins, also resulting from a full cousin mating, were mentally retarded, one of them had congenital vitium cordis and polydactyly. Father, 52 years old, sloping audiogram till 40 db loss of hearing. May be presbycusis. Bone conduction as air conduction. Mother normal.

No. 5. One deaf child. Father normal. Mother: somewhat too low in the high tone range. A cousin of the child is deaf, too.

No. 6. Two deaf cousins. First child: parents double first cousins. Father: at both sides a dip of 40 db at 4000 Hz, probably of traumatic origin. Mother normal. Second child: father: dip of 40 db at 4000 Hz (traumatic?). Mother normal. A daughter of a brother of the father is deaf, too.

No. 7. One deaf child. Parents *second* cousins. Father, 37 years old, *severe loss of hearing in the high tone range, probably congenital*. Bone conduction as air conduction. Mother: slight high tone loss of hearing in the right ear. Bone conduction as air conduction.

2. Parents not cousins,
but in each marriage more than one sibling born deaf

No. 8. Two marriages, the fathers are brothers. First marriage: two deaf children. Father normal. Mother, 42 years old, precipitated presbycusis? Sloping audiogram till 50 db loss of hearing. Bone conduction as air conduction. Second marriage: three deaf children. Father: left ear a dip of 40 db at 4000 Hz, must be acquired. Mother: left ear a dip of 40 db at 8000 Hz, must be acquired, too.

No. 9. Four deaf children, nearly no remnants of hearing. Parents normal.

No. 10. Three deaf children. Father and mother in the right and left ears a dip of 40 db at 4000 Hz. Must be acquired.

No. 11. Three deaf children. Father: loss of hearing caused by otitis media duplex. Bone conduction normal. Mother normal.

No. 12. Two deaf children. Father, 35 years old, at left ear loss of hearing at 8000 Hz 40 db. Precipitated presbycusis? Curiously, his right ear completely deaf. He was not aware of it! Cause unknown. Mother: dip of 60 db at 4000 Hz. Traumatic?

No. 13. Two boys *suffering from severe hearing impairment*. Parents normal.

Though many parents show some impairment of hearing, e.g. dips *, there is only one parent (no. 7, father) who has most probably a congenital loss of hearing. The great difficulty is that so many causes may

* As of course men more often are exposed to noise, which often alters the audiogram, fathers are of lesser value than mothers in detecting a possible "heterozygous audiogram".

change the hearing acuity. Slight, or even severe traumata may be unknown and alter the threshold audiograms. If we suspect e.g. a dip to be of traumatic origin, we nearly never know at what age that trauma occurred and the dip appeared in the audiogram. Most otologists regard that dip as a result of exposure to the influence of noise. Theoretically however we cannot even say with certainty, that the dip was not congenital! Furthermore there may be a precipitated presbycusis. Of course it is not impossible that precipitated presbycusis appears more frequently in heterozygotes than in homozygous normally hearing individuals. It is also conceivable that "heterozygous ears" are more liable to acoustic traumata than "homozygous normal ears", but these are only suppositions.

The conclusion of my investigation is that the 30 normally hearing parents of children suffering from recessive deafness are *not* detectable as heterozygotes. Putting the matter more strongly; as a result of my investigation and of those of the authors mentioned, and taking into account the difficulties developed above, *I think it is impossible to solve this problem audiometrically.*

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Discussion

J. van den Bosch (Leiden): As the object of Dr. Wildervanck's very interesting investigation was a limited one, i.e. to see if there exists a 100% *recognizability* in the parents of children with hereditary recessive deafness, this same limitation should in my opinion be found both in the title and in the conclusion of his paper. The question in the title "Are the parents of deaf children detectable as heterozygotes?" and the answer in his conclusion "The parents are not detectable as heterozygotes!" suggests, that his investigation justifies this conclusion, as if none of the parents of deaf children in general would be detectable. From the fact, that 18 of the parents had a normal audiogram the only conclusion to be drawn is, that in Dr. Wildervanck's material the *recognizability* of the parents is probably less than 60%. The only information, yielded by this figure, as regards all other parents of deaf children, is that the *recognizability* in general will probably be less than 100%. How much less than 60% the *recognizability* is in Dr. Wildervanck's

material could only be estimated by the incidence of abnormal audiograms among parents of deaf children, as compared to the incidence of abnormal audiograms among parents of the same age-agroup of children with normal hearing. Such a comparison could give an idea of the significance of the abnormal audiograms, which Dr. *Wildervanck* found. As much of the progress we hope to make in gaining recognition for Human Genetics as an indispensable branch of medicine will depend for a considerable part on the extent, to which we will be able to find more and better methods of disclosing "latent" carriers in general, it seems to me, that such an investigation would be of great importance.

L. S. Wildervanck (Groningen): Of course it has not been *significantly* proved that presumably heterozygotes are not detectable as such, but one who has seen—and I did—many audiograms of arbitrary persons, will agree that the aberrations which the parents of my patients show in their audiograms, are very common. And together with the individuals examined by the authors mentioned by me, a number of about 60 or 70, showing all non-characteristic audiograms, there will be one of them which may perhaps point to a congenital hardness of hearing.

My investigation was not at first instance for scientific, but for practical purpose, i.e. for genetic counselling. And for this purpose the results of my investigation supplement those of the investigators mentioned.

The fathers being more exposed to the influence of noise are of lesser value than the mothers, but should certainly not be neglected.

PROCEEDINGS OF THE FIRST INTERNATIONAL CONGRESS OF HUMAN GENETICS

Copenhagen, August 1-6, 1956

Edited by

TAGE KEMP

President of the Congress

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Secretary General

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Vice-Secretary General

PART V



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HEREDITARY ABNORMALITIES OF THE EYE

Franceschetti, A., and D. Klein: Acta genet. 7, 255-259, 1957

Ophthalmological University Clinic, Geneva, Switzerland

TWO FAMILIES WITH PARENTS OF DIFFERENT TYPES OF RED-GREEN BLINDNESS

By A. FRANCESCHETTI and D. KLEIN

In 1876, *Horner* published two pedigrees of red-green blindness showing a mode of inheritance analogous to that set forth by *Nasse* (1820) for haemophilia, that is to say, transmission from grand-father to grand-son through daughter-carriers, themselves clinically healthy. He had also already explained the apparently paradoxical appearance of a transmission from father to son in one of his pedigrees by showing that the mother was the carrier.

Proceeding from the discovery by *Morgan* and his school (1910-1913) of sex-linked inheritance in *Drosophila*, *Wilson* (1911) was able to relate the laws of *Nasse* and *Horner* to the presence of a sex-linked gene.

Thanks to Nagel's anomaloscope which allows of quantitative analyses of the various disturbances of the chromatic sense, red-green blindness has become one of the best examples of multiple allelism studied in man.

One must distinguish between two groups of colour-blindness: on the one hand for red, represented by protanopia (P), extreme protanomaly (EPA), protanomaly (PA), and on the other hand for green, represented by deuteranopia (D), extreme deuteranomaly (EDA) and deuteranomaly (D).

Following the studies of *Döderlein*, *Just*, *Waalder*, *Franceschetti*, *Brunner* and others, it has been confirmed that the normal gene is dominant over the genes responsible for the different forms of red-green blindness and that the gene responsible for a slight anomaly is dominant over that responsible for a more serious form.

The genes of the protanopic series are therefore allelomorphous to each

other, as are also the genes of the deuteranopic series. One can thus establish two series of multiple alleles with their respective dominance:

$$N > PA > EPA > P$$

$$N > DA > EDA > D$$

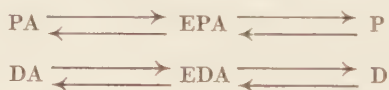
But what is the relation between the protanopic and the deuteranopic series?

Credit must be given to *Waal*er for his theory that the genes of the protanopic series and those of the deuteranopic series are not allelomorphic to each other, and that they must therefore be located in different loci of the chromosome.

This theory affords an explanation for the following observations:

(1) that a woman who has received a protanopic gene from one parent and a protanomalous gene from the other, is phenotypically protanomalous;

(2) that all intermediary forms within the two series can be observed and not only steps from the slight to the severe form, but also from the severe to the slight, since these polyalleles are rather unstable:



(3) that, on the other hand, an intermediary form between the protanopic and the deuteranopic series has never been observed;

(4) that a woman with one protanopic and one deuteranopic son, who must therefore carry a protanopic gene on one of her X-chromosomes and a deuteranopic gene on the other (*Göthlin, Waaler, Brunner*) is not herself deprived of chromatic sense, even though she must be considered homozygous, if no distinction is drawn between the two types of red-green blindness;

(5) that the statistical frequency of red-green blind women in the general population does not correspond to the theoretical calculations based on the frequency of red-green blindness in men. In fact, granting a frequency of red-green blindness in man, as revealed by the investigations of *Waal*er in Norway, and of *von Planta, Wieland, Franceschetti* in Switzerland, of about 8%, the number of women clearly affected ought, theoretically, to be 0.64%. In actual fact, only about 0.4% women are red-green blind. This discrepancy may be accounted for by the fact that there are women with two different genes on their X-chromosomes who are not phenotypically affected. On the other hand, by calculating only the theoretical frequency of homozygous women with two genes of the same group

(allelomorph-compound), while omitting those with a gene of the protanopic series and a gene of the deuteranopic series, one arrives at a frequency of 0.38 %, a figure much closer to that obtained statistically (0.43 % according to *von Planta*). The slight surplus of the statistical frequency may be explained by the occasional phenotypical manifestation of red-green blindness in heterozygous women.

Thus, all the known facts agree with the theory of multiple allelism within each protanopic and deuteranopic series, but non-allelism between the two series.

For a long time these results were based on the identification of doubly heterozygous women (non allelomorph-compound) through their sons being affected with two different types of red-green blindness. However, the direct proof of *Waller's* theory was lacking, which is that daughters of parents with different types of red-green blindness ought to be phenotypically normal.

However, the probability of finding a married colour-blind couple was slight. For Switzerland, we calculated that the theoretical probability of a marriage between two individuals with the same type of red-green blindness was 2:10,000, and of a marriage between two individuals with different types only 1:10,000. These unions are therefore rare, especially if one considers that one must, moreover, find couples with daughters to examine (preferably with sons as well).

In 1949, after more than twenty years of research, we at last discovered a couple conforming with all these requirements. The father was protanopic, the mother deuteranopic. From this union were born four children of whom three were sons, deuteranopic like the mother. The daughter, who had received a deuteranopic gene from her mother and a protanopic gene from her father, did not show the slightest trace of colour-blindness, either in the Ishihara test, or on examination with the anomaloscope.

Thus, for the first time, confirmation was obtained that women with a protanopic gene on one of the X-chromosomes and a deuteranopic gene on the other, are phenotypically normal.

In 1953, four years after this observation, we were fortunate enough, by an extraordinary coincidence, to detect another couple. In this case the anomaloscope revealed that the husband was deuteranopic and the wife protanopic.

Moreover, in the pedigree of this family, particularly on the maternal side, there are a great number of other cases of colour-blindness which we have not yet fully checked.

This couple has two daughters, the elder at present nine years old and the younger seven. Unfortunately, they are still too young to be examined with the anomaloscope, but the Ishihara test reveals no disorder of the chromatic sense in the elder child. As for the younger, the parents stated that she was quite normal and that she even corrected her colour-blind parents' mistakes.

Thus, we have been able to fill the last gap in the observations confirming *Waalers*' two-loci theory.

I should also like to mention that, according to the theory put forward by *Just* and *Lenz*, there is no question of two allelomorphic series in different loci of the chromosome, but of a single series of multiple alleles located on the same locus. According to this conception the protanopic and deuteranopic series are merely degrees of mutations in different tendencies. The reason for a normal chromatic sense in the doubly heterozygous woman (for the two types of colour-blindness) is neutralization or compensation of two genes with divergent effects.

This theory has not yet been refuted. It is, however, difficult to imagine that a protanopic gene, responsible for a serious anomaly, might be neutralized if on the other chromosome there is a deuteranomalous gene, giving rise only to a slight anomaly.

A direct proof of *Waalers*' theory of two loci could be found only if, for example, in the two families we have just discussed, the daughters, doubly heterozygous but with a normal chromatic sense, would eventually have a son with a normal colour sense, whereas theoretically they could have only deuteranopic or protanopic sons. We would then be in the presence of a crossing-over and this fact would in itself definitely prove *Waalers*' theory of two loci.

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Discussion

W. Jaeger (Heidelberg): Daß die Verhältnisse leider nicht immer so klar und übersichtlich liegen, wie bei den beiden von *Franceschetti* und *Klein* demonstrierten Familien, konnte ich an einem anderen, sehr eigenartigen Stammbaum zeigen (v. *Graefes*: Arch. f. Ophth. 151, 229-248, 1951). In einer Reihenuntersuchung bei Angehörigen der Heidelberger Universität haben wir zwei Brüder gefunden, wovon der eine deuteranomal, der andere protanop war. Die Mutter dieser beiden Brüder war nun zweifellos *nicht* normal farbensichtig, obwohl sie mit Ishihara keine Fehler machte. Am Anomaloskop gelang ihr

überhaupt keine Gleichung. Die Gleichung größter Ähnlichkeit lag im Bereich der Einstellung der Deuteroanomalien. Sonstige Untersuchungen am Spectrum ergaben außerdem noch eine Störung im Bereich zwischen grün und blau, ähnlich wie bei einer Tritanomalie. Die Farbensinnstörung dieser Frau ließ sich überhaupt in kein Schema der bisher bekannten Typen angeborener Farbensinnstörungen einordnen. Merkwürdigerweise hatte nun die Schwester dieser Frau eine Protanopie (mit zusätzlicher Herabsetzung des Blaugelbsinns). Der Sohn dieser protanopen Frau war dagegen wieder deuteranomal. Daraus geht hervor, daß in dieser Familie zwei Fälle von nicht allelomorph-Compound in der Kombination Protanopie + Deuteranomalie vorhanden sind. Sie haben beide eine manifeste Farbensinnstörung: Die eine in einer Form, die mit Hilfe der bisherigen Typeneinteilung überhaupt nicht zu klassifizieren ist, die andere hat eine Protanopie.

Wir halten es für möglich, daß man dieses eigenartige Verhalten damit erklären muß, daß bei diesen beiden Frauen auch noch eine Störung der 3. Komponente (Tritodefekt) aufgetreten ist und auf diese Weise bei der Kombination Protanopie + Deuteranomalie nicht ein normaler Farbensinn entsteht, sondern jeweils eine der beiden Störungsformen des Rot-Grünsinns manifest geworden ist.

A. Franceschetti (Geneva): The interesting genealogical tree presented by *Jaeger* gives no answer to the question of the one or two loci-theory of protanopia and deuteranopia. The fact that the two double heterozygous sisters have both anomalous colour-vision may be explained by the action of a familial factor.

Ruffie, J. and R. Huron: Acta genet. 7, 259-263, 1957

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SUR L'HÉRÉDITÉ DU DALTONISME NOUVELLE OBSERVATION D'UNE FRATRIE ISSUE DE DEUX DALTONIENS DE TYPES DIFFÉRENTS

Par J. RUFFIE et R. HURON

Le mécanisme héréditaire des troubles de la vision colorée est encore sujet à discussions. Certains auteurs admettent que les gènes conditionnant les différents types de daltonisme rouge-vert sont des allèles multiples d'une seule série portée sur le chromosome X [7 et 8]. D'autres pensent qu'il existe deux séries de gènes allèles portés par deux locus

étroitement liés sur le chromosome X [1, 2 et 10]. Dans cette hypothèse, on admet en général que le gène occupant un locus conditionne la vision du vert et ses mutations les troubles de la vision du vert: deuteranomalie (affaiblissement de la vision du vert) et deuteranopie (cécité pour le vert).

Par ailleurs, le gène occupant l'autre locus conditionnerait la vision du rouge et ses mutations les troubles de la vision du rouge: protanomalie (affaiblissement de la vision du rouge), protanopie (cécité pour le rouge).

Quelle que soit la théorie adoptée, le caractère normal domine le caractère aberrant.

Si cette deuxième théorie correspondait à la réalité, une femme possédant un seul gène daltonien de l'une des séries et un seul gène daltonien d'une autre série, aurait une vue normale, chaque gène muté étant masqué par l'allèle normal dominant.

Cette théorie expliquerait le cas rapporté par *A. Franceschetti* et selon lequel une fille issue de parents présentant deux types de daltonisme différents peut être phénotypiquement normale [10]. Sous réserve d'illégitimité, cette observation paraît hautement démonstrative *.

Par ailleurs, l'on admet communément que, au sein d'une même série polyallélique, le caractère normal domine tous les caractères daltoniens et parmi ces derniers, toute forme moins mutée domine les formes plus mutées.

Il nous paraît intéressant de rapporter ici le cas d'une famille de daltoniens, chez laquelle on rencontre deux degrés différents de troubles portant sur le vert.

Cette observation semble remettre en cause le sens de la dominance communément admis.

La famille étudiée comprend: le père (Jean); la mère (Maria) et trois fils (André, 20 ans; Michel, 15 ans; Jean-Claude, 8 ans).

Tous présentent des anomalies de la vision colorée qui ont été définis en moyen des tests d'Hishihara.

Le résultat de ces tests pour les différents membres de la famille est le suivant (Tableau 1):

Ces résultats démontrent que:

1. La mère Marie, les fils André et Jean-Claude présentent un type de daltonisme vert complet, identique chez les 3 sujets.

* Il nous paraît souhaitable d'effectuer dans toutes les constellations familiales ainsi étudiées, la recherche du plus grand nombre possible de facteurs sanguins, afin d'éliminer au maximum les chances d'illégitimité.

Tableau 1

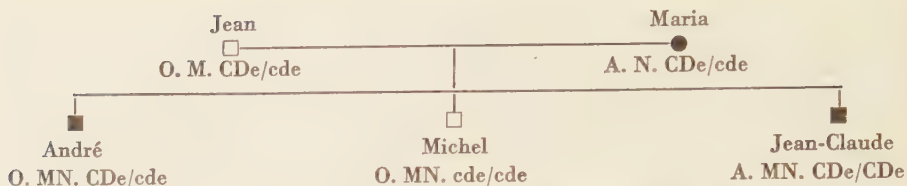
Tableau n°	Jean lit	Maria lit	André lit	Michel lit	Jean-Claude lit
1	12	12	12	12	12
2	3	3	3	3	3
3	5	5	5	5	5
4	70	70	70	70	70
5	85	35	35	85	35
6	2	2	2	2	2
7	5	5	5	5	5
8	17	17	17	17	17
9	21	21	21	21	21
10	—	—	—	—	—
11	—	—	—	—	—
12	8 (?)	—	—	87 (?)	25 (?)
13	45 (?)	—	—	5 (?)	15 (?)
14	5	—	—	—	—
15	7	—	—	—	—
16	—	—	—	—	—
17	—	—	—	—	—
18	5	5	5	5	5
19	8	8	8	2	2
20	45	45	45	45	45
21	23	73	28	73	75
22	26	2	2	26	2
23	48	4	4	42	42
24	35	3	85	35	3
25	96	9	96	96	9

2. Le père Jean et le fils Michel présentent un daltonisme incomplet (mais dont le type exact est difficile à définir par les seuls tests d'Hisshihara).

On n'a pu tester les grands-parents, mais le père, B. Jean, a un frère et une sœur qui ont une vision colorée normale.

On ne rencontre aucune autre anomalie héréditaire dans cette famille, soit liée au chromosome sexuel, soit autosomale.

Nous avons étudié les groupes sanguins des différents membres de cette constellation. Aucune impossibilité de filiation n'a été constatée. Le tableau généalogique suivant figure nos résultats:



(les sujets deuteranopes sont figurés en noir, les daltoniens incomplets sont blancs)

Fig. 1

Discussion

L'étude de la famille B. indique que la mère possède deux chromosomes X portant des mutations différentes. En effet, l'un de ses chromosomes X porte le gène conditionnant le daltonisme vert complet et l'autre chromosome X porte le gène conditionnant un daltonisme partiel. Ce chromosome est aussi possédé par le père. La mère a transmis le premier chromosome à ses fils André et Jean-Claude le deuxième chromosome à son fils Michel.

Le fait que la mère ne soit pas phénotypiquement normale démontre que ses deux chromosomes X portent deux mutations constituant des gènes allélomorphes.

Dans ce cas, si la théorie selon laquelle toute forme moins mutée domine la forme plus mutée correspondait à la réalité, la mère Maria serait du type daltonien incomplet, comme son fils Michel. Or la mère, étant phénotypiquement daltonienne vert complet, bien que génotypiquement hétérozygote, il semble logique d'admettre que dans ce cas le caractère le plus muté (vert complet) présente une dominance absolue sur le caractère le moins muté (daltonisme incomplet) — contrairement à ce qui est communément supposé.

Un dernier point reste à examiner:

Certains auteurs [9] ont émis une hypothèse suivant laquelle les mutations correspondant aux différents degrés de daltonisme seraient des «mutations spatiales» affectant seulement diverses fractions du gène comme cela a été décrit pour les mutations *scute* de *Drosophila melanogaster* [5] et existe sans doute pour le facteur D^u du système Rhésus rencontré dans l'espèce humaine [6].

S'il en était ainsi, l'hybridation entre deux mutations différentes du gène normal (ce qui est réalisé chez la mère Maria B.) entraînerait un retour, au moins partiel, au type normal. En effet, dans ce type de mutation, on admet que le gène est formé de plusieurs fractions ayant chacune une

fonction déterminée et pouvant muter pour leur propre compte, d'une manière tout à fait indépendante. La fraction non mutée continue à assurer sa fonction normale.

On conçoit très bien que, dans ce cas, l'hétérozygote porteur de deux mutations différentes, puisse faire plus ou moins retour au type normal, la partie non mutée d'un gène dominant la partie mutée du gène alléomorphe.

Cette disposition devrait entraîner une vision à peu près normale. Or il n'en est rien puisque Maria B. est deuteranope typique. Cette théorie des mutations spatiales ne peut ici être retenue.

Conclusion et résumé

L'étude d'une nouvelle fratrie issue de deux daltoniens de type différents semble indiquer que le gène conditionnant une anomalie grave (type de daltonisme complet) peut être dominant sur le gène conditionnant une anomalie légère (type de daltonisme incomplet), contrairement à ce qui a été longtemps admis.

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DYSCHROMATOPSIES ET GÉMELLITÉ MONOZYGOTE

Par R. KHERUMIAN et J. MOULLEC

Les dyschromatopsies figurent parmi les caractères classiques de la génétique mendélienne. De très nombreuses observations ont pleinement confirmé la localisation sur le chromosome X des gènes qui les contrôlent. De plus, il y a d'excellentes raisons d'admettre la conception de *Waal* de deux loci (séries protane et deutane) et de multiples allèles avec la dominance de la vision normale sur l'anomalie et de l'anomalie faible sur l'anomalie plus accentuée.

L'observation de deux paires de jumeaux monozygotes que nous présentons au Ier Congrès International de Génétique Humaine s'ajoute à d'autres observations similaires, en montrant la concordance de l'anomalie chez les partenaires du couple. Nos deux observations n'offrent aucune particularité notable, sauf peut-être la rigueur du test de la monozygotie. Si néanmoins nous avons cru opportun de la communiquer, c'est essentiellement à cause de quelques réflexions qu'elles semblent devoir susciter.

Lorsqu'on compare point par point les réactions des jumeaux MZ aux différents tests à couleurs pigmentaires ou à couleurs spectrales, on constate que la concordance est quasiment parfaite, sans aller toutefois jusqu'à l'identité absolue. Les différences sont faibles et sont de l'ordre des différences que l'on observe chez le même dyschromate lors des retests successifs.

Donc du point de vue génétique l'examen de jumeaux fournit une parfaite confirmation de la nature rigoureusement héréditaire et strictement définie des dyschromatopsies. Par contre, si l'on considère le problème du point de vue du mécanisme physiologique de l'anomalie, on constate que dans les deux cas – comparaison des partenaires du couple gémellaire, comparaison des retests du même dyschromate – il existe une certaine

marge dans l'étendue des confusions, marge fort étroite chez les dichromates, plus étendue chez les trichromates anomaux. Elle est facile à mettre en évidence par des tests à couleurs pigmentaires. Dans les égalisations chromatiques faites par des trichromates anomaux, l'attitude psychologique du sujet, sa volonté de donner une réponse précise, sa sincérité même sont des facteurs apportant quelque élément de trouble. Chez les dichromates qui acceptent des égalisations les plus variées, la comparaison des égalisations successives perd naturellement presque tout intérêt.

L'existence d'une certaine marge dans les confusions commises par des dyschromates serait certainement d'explication aisée si nous possédions une théorie indiscutable de la vision chromatique. Tel n'est pas le cas, plusieurs conceptions rivales cherchant à interpréter les faits, mais aucune n'étant satisfaisante sans d'importantes réserves.

Nous sommes ainsi en présence d'une situation quelque peu paradoxale. Le mécanisme génétique des dyschromatopsies est parfaitement connu et la rigueur de son action ne semble pas comporter d'exceptions. Par contre, les manifestations phénotypiques de ce mécanisme n'apparaissent pas sous la forme de phénomène unitaire aux contours rigoureusement définis, mais comme une sorte de déviation, assez vaguement circonscrite, du sens chromatique. Les techniques employées pour mettre en évidence les dyschromatopsies ne laissent pas saisir la nature exacte du trouble, organique ou fonctionnel, de la rétine dont l'origine génétique est cependant parfaitement établie.

L'interprétation du mécanisme de la vision chromatique pourrait dès lors bénéficier de l'analyse approfondie des dyschromatopsies. Toutefois, cette analyse devrait être dégagée de l'imprécision que comportent les réponses des dyschromates. L'élimination de facteurs psychologiques subjectifs pourrait probablement s'obtenir par une combinaison judicieuse de deux méthodes habituelles d'examen du sens chromatique: méthode de confusion (à l'aide de couleurs pigmentaires) et méthode d'égalisation par des lumières monochromatiques. Il serait souhaitable de concevoir un appareil où les images de confusion seraient produites par des lumières convenablement choisies, ce qui permettrait une analyse précise des déficiences rétiniennes chez les dyschromates. On pourrait ainsi approcher des unités physiologique que contrôlent les gènes et, partant, édifier la théorie générale de la vision chromatique.

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HEREDITY OF DISC-SHAPED CATARACT

By J. FRANÇOIS and E. DeVOS

The disk-shaped cataract (*Collins and Mayou* [1925]), also called "Ring-katarakt" (*von Szily* [1928]) and "annular or umbilicated cataract", was described for the first time by *Becker* in 1883. It is rare, as only about thirty observations are to be found in the literature. It must not be confused with congenital membranous cataract, due to the degeneration and resorption of a lens while in the course of formation, and often secondary to other ocular anomalies.

(1) *Clinical aspect*

Annular cataract has the form of a dumb-bell or a lifebuoy. Three parts may be recognized in it: (a) *A central part*, constituted by a greyish membrane, which, in consequence of the absence of the crystalline nucleus, is shrunken away from the other parts of the crystalline lens: thus there exists in the centre of the latter a depression more or less marked, whence the name "umbilicated cataract".

The central membrane, with a diameter equal to that of the embryonic nucleus, that is, about 2 to 3 mm., is rather thin, as it is not more than 0.5 mm. thick. As it is opaque and presents an irregularly undulating surface, it fairly resembles a secondary cataract.

(b) *Around this central part*, the crystalline lens is normally developed and forms a more or less opaque ring ("annular cataract"), having the thickness of a normal lens. This ring is not always completely opacified; some parts may be partially transparent; opacities of variable density and irregular form may also be found.

(c) *The most peripheral part* is often clear, but there may be found either cuneiform opacities (*Rizzini* [1953]) or, more often opacities in concentric layers of the zonular type (*Haro* [1946]; *Rizzini* [1953]).

In brief, annular cataract is characterized essentially by absence from the beginning of the crystalline lens nucleus. Due to this fact, the lens is narrow, especially at the level of its central part, and is, at the same time, smaller (microphakia). The absence of the nucleus is nearly always total, sometimes, however, it is incomplete, as in case 2 of *Franceschetti, Forni* and *Rizzini*: the central part then maintains a certain thickness and the excavation at its level is less pronounced but more irregular. It also happens sometimes that there is produced a partial and spontaneous resorption of the existing crystalline masses, which has as a result a widening of the central membrane (*von Szily* [1928]; *Haro* [1946]). It is no wonder, that there exists sometimes a deepening of the anterior chamber, and that there is at the same time an iridodonesis, because the volume of the lens is reduced in annular cataract.

The affection is nearly always bilateral; there are, however, a few exceptions (*Oguchi* [1931]; *Rizzini* [1953], case No. 2).

In nearly half the cases it is associated with a congenital ectopia of the lens: the subluxation is also bilateral, always symmetrical and generally superonasal (*von Szily* [1928], *Vázquez Barrière* [1939], *Malbrán* and *Tosi* [1940], *Haro* [1946], *Franceschetti, Forni* and *Rizzini* [1952]). In this connection it is interesting to report that, in the unilateral case of *Oguchi* [1931], there occurred a spontaneous luxation of the lens in the other eye.

There often exists also an aplasia or a hypoplasia of the fovea (*von Szily* [1928]), which explains the bad vision as well as the "searching nystagmus", which persists even after a successful operation. Thus *Haro* [1946] only obtained a postoperative vision of 1/10 in one case, of 15/100 in the right eye and of 15/70 in the left eye, in a second case, of 20/70 (right eye) in a third case; *Rizzini* only obtained 3/50 in the right and 1/10 in the left, in his first patient.

In true primary annular cataract there exist no other ocular anomalies than those we have just mentioned: *von Hess* [1905], *von Szily* [1928] 4 cases, *Bücklers* [1929] 2 cases, *Oguchi* [1931], *Vázquez Barrière* [1939], *Malbrán* and *Tosi* [1940], *Haro* [1946] 16 cases, *Sautter* [1951] 2 cases, *Rizzini* [1953] 2 cases.

The four cases reported by *Vossius* [1893], *Collins* [1898], *Marchesani* [1930] and *Goldfeder* [1934] belong rather to the membranous or secondary cataracts (Soemmering's ring): the absence of the lens nucleus is not primary, but secondary to a spontaneous resorption following a lesion of the anterior capsule (secondary cataract) or of the posterior capsule (membranous cataract). *Vossius* [1893] found a cataract in a lens, in which the nucleus was absent and the central part was flattened, in a blind eye,

that had an adherent corneal leucoma and had been enucleated for aesthetic reasons.

Collins [1898] observed the same lens in a buphthalmic eye, which he enucleated in a little girl of 7 years.

Marchesani [1930] found it in an eye presenting a pronounced corneal staphyloma. *Goldfeder* [1934] saw it associated with a persistent pupillary membrane.

(2) *Histopathological examination*

In section an annular cataract has the form of a dumb-bell: two lateral masses are seen united by a central band, thin and membranous (*von Hess* [1905], *von Szily* [1928], *Haro* [1946], *Sautter* [1951]). The lateral masses are of variable thickness from 2.5 to 6 mm., the central band 0.5 mm. thick.

The principal characteristic is the absence of the nucleus, so that, in the central part, the anterior crystalloid approaches the posterior crystalloid: between these two membranes of normal appearance, although the capsule is absent or badly formed at the level of the posterior pole, residues of the crystalline lens epithelium are found, as well as an eosinophile and slightly fibrillary mass, in which fusiform cells are seen, isolated or grouped in threes or fours: in some places in certain cells there is observed a vacuolisation of the cytoplasm that is also eosinophile: there are no mitoses (*Haro* [1946]).

In the lateral masses normal epithelium and recognisable lens fibres are found, which are, for the most part, degenerated and vacuolised, less on the equatorial than on the central area.

The other parts of the eye (uvea, retina, etc.) are quite normal.

(3) *Pathogenesis*

For *von Hess* [1905] annular cataract is a central cataract which is resorbed to the point of complete disappearance. For *Ida Mann* [1935] a considerable disturbance must be postulated, preventing the formation of the primary fibres and acting in the course of the 5th week of embryonic life. The aplasia is not, however, final, because the development of the secondary fibres can go on normally.

The existence of several familial cases (*von Szily* [1928]) and hereditary cases (*Haro* [1946]) makes this explanation plausible.

(4) *Heredity*

Von Szily [1928] observed an annular cataract in four members of a family of nine brothers and *Bücklers* [1929] in two sisters.

Haro [1946] has found 16 cases in a family group of 59 persons, among which the affection was transmitted through 3 generations by an apparently autosomal dominance.

The fact that in this family no man transmitted the disease to his sons, but only to his daughters, and the fact also that the women affected are much more numerous than the men (11:5) suggests the possibility of a dominant heredity bound to the chromosome X.

(5) Treatment

Haro [1946] advises the performance in a first stage of a discission to bring about the resorption of the crystalline substance present and to excise the central membrane with De Wecker's scissors in a second stage.

Certain authors have tried to do a total extraction. This is difficult and even dangerous, for the central part is sometimes adherent to the hyaloid membrane, which accounts for the loss of the vitreous as in Malbrán and Tosi's case [1940].

(6) Personal observations

We have had the opportunity to examine a family in which seven members presented a cataract, probably annular (Fig. 1).

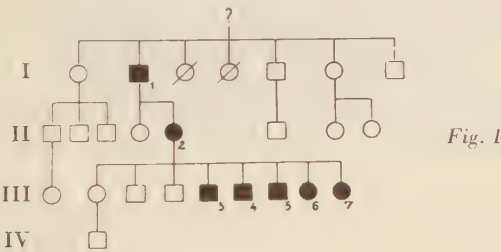


Fig. 1

First generation. – Two girls died at an early age and we have not been able to obtain any information about them. Of the five other members, all brothers, only the eldest brother was affected by a congenital bilateral cataract, for which he was operated on at the age of 17 with a good functional result.

Second generation. – The children of the unaffected members of the preceding generation are all unaffected. The member affected (I₁) has two daughters, one exempt and the other affected (II₂).

The latter has been operated on at the age of 14 years. Ocular examination reveals a bilateral aphakia with persistence of a transparent membrane, loaded with scattered pigment on the right side, less pigmented on the left, where she presents a few less opaque striae. There was no iridectomy; the pupil is oval on the right while it is well rounded to the left, there are no other ocular anomalies. The vision is 10/10 in the right eye and 9/10 in the left after correction.

Third generation. — II₂ has eight children. The three eldest do not present any anomaly of the lens; the second is hypermetropic (right eye and left eye: +5 D.)

The fourth child, Paul (III₃), is now aged 24 years. A congenital cataract was diagnosed at the age of 4 months and operated on at the age of 3 years. At the present time there is: a horizontal nystagmus, an alternating supero-internal strabismus, an incomplete microcornea (diameter of 10.5 mm. in both eyes), a heterochromia of the iris (grey iris on the right, brown on the left), a deeper anterior chamber on the right than on the left; the lenses are reduced to an opaque membrane, denser and thicker at the periphery than at the centre, fairly pigmented, especially at certain places. The fundus is not explorable. The vision is 2/10 on the right and 1/50 on the left after correction of the aphakia. It is obviously difficult here to state whether it is a secondary cataract or an annular cataract, as the patient was operated on in his early age.

The fifth child, Albert (III₄), is aged 22 years. At the age of 3 years he was operated on for cataract of the right eye with a bad result. At the age of 13 years he was operated on the left eye with a result equally bad. At the present time the two eyes are, in fact, atrophic: the two corneas are dull and vascularized, they present a girdle opacity. There is not even light perception.

The sixth child, André (III₅), is aged 21 years. At the age of 13 years he was operated on for congenital cataract in the right eye: total iridectomy, secondary cataract, external strabismus, vision reduced to 1/50. The left eye has never been operated on: an annular cataract without ectopia is found there: the central part is thin, but very opacified: it is surrounded by a clearer ring, which is itself surrounded by a ring that is opaque and much thicker: the extreme periphery is partially transparent and thinner. There are no other ocular anomalies, the corneal diameter is 11 mm. the vision is 6/10 after correction.

Françoise (III₆) is aged 17 years: she is affected by congenital cataract in both eyes, but she has never been operated on. She presents a horizontal nystagmus with incoordination of the ocular movements, but without

strabismus in the strict sense. The corneal diameter is 11 mm. on both sides. The iris is normal; the pupils are free and react well. An annular cataract without ectopia is observed on both sides (Fig. 2), the central part is rather thin and opaque; it is surrounded by a somewhat thicker ring, containing numerous gross opacities, the extreme periphery is less thick and at the same time clearer. The fundus of the eye is difficult to explore. The vision is reduced to 1/100 on the right and 1/25 on the left. It was sufficient to incise the rudimentary lens to obtain a sufficient pupillary opening, but the functional improvement was not much, doubtless in consequence of an aplasia of the fovea. The vision is at present 1/50 on the right and 1/20 on the left (after correction 13 D).

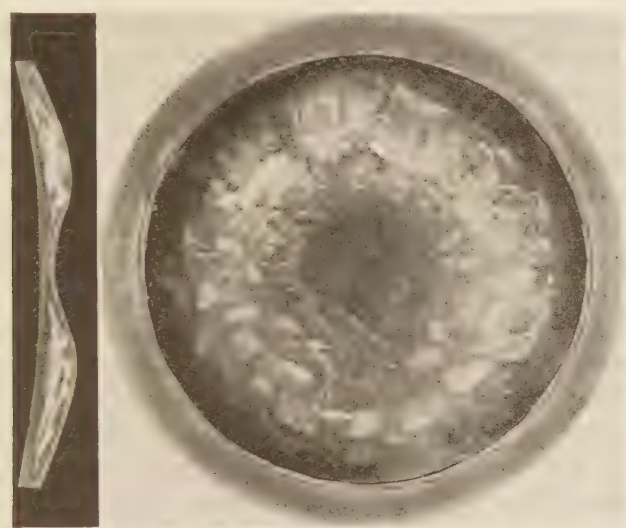


Fig. 2

Bernadette (III₇) is aged 14 years. She is also affected by bilateral congenital cataract, but has never been operated on. There is no nystagmus, but an external concomitant strabismus of the left eye. The corneal diameter is 11 mm., on both sides. The iris is normal; the pupils are free and react well. On both sides a cataract more membranous than annular is seen, without ectopia: between the anterior and posterior capsules, which are very thin, very close to one another and apparently intact, are to be seen irregularly disseminated opacities and multicoloured flecks, more numerous on the right than on the left. It is known, however, that in annular cataract there may be a partial and spontaneous resorption of the existing crystalline lens masses (*von Szily, Haro*). The fundus, difficult to

explore, appears normal. The vision is 1/20 on the right and 1/100 on the left. A simple incision of the crystalline membrane gave a pupillary gap of fair size. Vision is at the present time 0.3 to 0.4 on the right and 1/20 on the left after correction (spher. + 12D = cyl. + 1 D vertical axis).

It is difficult to know which was the exact type of the cataract with which the grandfather, the mother, Paul and Albert were affected, because they were all operated on. On the other hand, if Bernadette presents a cataract rather of the membranous type, André and Françoise certainly present a cataract of the annular type.

Although Cordes has been able to observe a membranous cataract in three members of the same family, the genetic nature of this form of cataract has not yet been proved. The hereditary factor is, on the contrary, much more obvious for annular cataract, as has been shown in the studies of *von Szily*, *Bücklers* and, above all, *Haro*.

For all these reasons we believe that we may say that in the family we have just described, we are dealing with an annular cataract, which is transmitted as an autosomal dominant rather as a sex-linked trait. It is true, we have no transmission from father to son, but at first the grandfather had only two daughters and no sons; then we have only three generations in our family; at last the women affected are as numerous as the men affected (3:4). For these reasons we may suppose that in the family of *Haro* the dominance was also autosomal and not linked to sex.

In conclusion we would say that in Françoise as well as in Bernadette, the only two patients that we have been able to operate on ourselves, the functional result is less good than the anatomical result in consequence, doubtless, of a foveal hypoplasia, which has, moreover, been established in the patients of *von Szily*, *Haro* and *Rizzini*.

In all our patients the crystalline lens anomaly was not associated with any other ocular anomaly, which constitutes an argument more in favour of the diagnosis of annular than membranous cataract.

Summary

The authors describe a family, in which an annular cataract is transmitted through three generations by autosomal dominance.

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Discussion

A. Franceschetti (Geneva): The demonstrated form of congenital annular cataract corresponds to the type described by von Szily (1928) as «Ringstarlinse», called in French «cataracte en bouée de sauvetage», in Italian «cataratta umbilicata». Together with Rizzini (Ophthalmologica 125, 342, 1953) we have emphasized a few years ago, that in the unique genealogical tree known till there (Haro: Arch. Ophth. 36, 84, 1946) no transmission from father to son had occurred. For that reason, a sex-linked heredity with manifestation in heterozygous women can not be excluded. It is the same for the genealogical tree demonstrated by the speaker.

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DÉGÉNÉRATION NODULAIRE DE LA CORNÉE (GROENOW) LIÉE A LA COULEUR DE L'IRIS (PEDIGRÉE D'UNE FAMILLE)

Par B. NIŽETIĆ et D. ŠAKIĆ

Le problème de l'hérédité multiple (*Riddel*), c'est-à-dire du comportement de plusieurs gènes pathologiques dans un arbre généalogique, n'a pas été, jusqu'à présent, suffisamment étudié, comme l'affirme le Professeur *Franceschetti* dans son rapport sur les aspects cliniques et sociaux de l'hérédité dans l'ophtalmologie, rapport présenté au XVI^e Congrès International d'Ophtalmologie à Londres.

D'une manière générale, on prétend que les gènes, lors de la liaison aux divers caractères pathologiques, ne manifestent pas de déviation de leur comportement habituel et se comportent comme s'ils étaient tout à fait indépendants les uns des autres.

De temps à autre, une ségrégation autonome de deux caractéristiques pathologiques peut être constatée après l'examen d'une seule famille. Mais, il existe des cas dont l'aspect est connu sous le nom de «*modification de dominance*». C'est ainsi que *Franceschetti* a eu l'occasion d'observer une famille atteinte de rétinite pigmentaire et d'otosclérose où il a pu constater une modification de dominance du gène récessif pour la rétinite pigmentaire due à l'influence des gènes responsables du défaut auditif.

Cette notion de «*modification de dominance*» s'accorde ainsi avec la théorie de *Beckerhaus* selon laquelle les formes dominantes de rétinite pigmentaire se manifestent sous l'influence d'un gène accessoire adjoint à l'agent récessif principal qui présente le type original. Se référant à ce problème, il serait peut-être intéressant de présenter l'arbre généalogique d'une famille atteinte de dégénérescence nodulaire (type Grænow) de la cornée et de rétinite pigmentaire toutes deux liées à la couleur de l'iris (Fig.1).

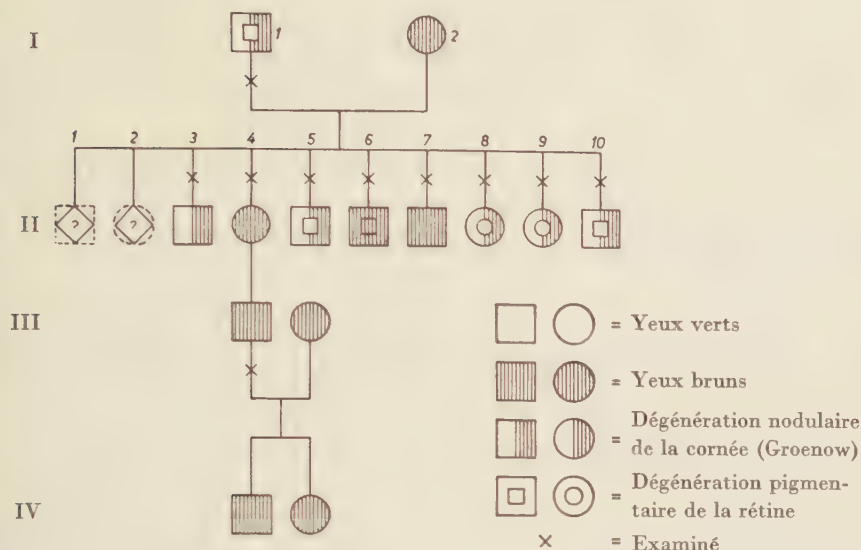


Fig. 1. Pedigrée de la famille Suić.

Observant cet arbre généalogique, soulignons les faits suivants:

1° Entre les parents, pas de consanguinité.

2° La dégénérescence de la cornée dans la famille S. en question se transmet dans deux générations d'une façon habituelle et simplement dominante. De même et comme il l'a déjà été exposé par divers auteurs, dans cette famille, la moitié des enfants (5 sur dix, 3 fils et deux filles) du père taré sont également atteints. On sait déjà que les descendants provenant des membres indemnes de telles familles restent sains sans exception. Le seul descendant de la 3e génération de cette famille est en effet tout à fait bien portant pour ce qui est de la cornée.

3° La forme de la dégénérescence pigmentaire appartient au type dominant qui est très rare (3-4 %). Elle se transmet dans la famille précitée dans deux générations, en général proportionnellement dans les deux sexes de la deuxième génération (3 fils et 2 filles). Nous tenons à faire remarquer que le «linkage» de cette forme de dégénérescence pigmentaire avec d'autres maladies de l'œil, comme par exemple l'hérédodégénérescence de la macule, le glaucome, a déjà été décrit, mais, à notre connaissance, il n'existe rien encore sur le «linkage» avec l'hérédodégénérescence de la cornée de type Groenow.

4° Le «linkage» de ces deux maladies avec la couleur de l'iris est également intéressant. Comme nous l'avons déjà signalé, tous les cas présentant une dégénérescence de la cornée (type Grænow), possèdent des iris bleu-clair-verdâtre.

Il en est de même pour les cas de la dégénérescence pigmentaire lorsqu'ils sont liés à la dégénérescence de la cornée tandis que le seul cas (II-6) possédant une dégénérescence pigmentaire et des cornées indemnes a les iris bruns foncés.

Tous les autres membres de la famille S. ont les iris bruns foncés. En ce qui concerne l'hérédité de la couleur de l'iris, elle n'est pas encore entièrement mise en lumière. En examinant cette question de la couleur de l'iris, on doit toujours prendre en considération qu'elle dépend d'une part du comportement de l'épithélium pigmenté et d'autre part de la pigmentation de la partie mésodermale de l'iris. D'après *Fischer*, dans les cas d'iris bleu il s'agirait d'une manifestation de domestication (*Domestikationserscheinung*) que l'on peut même observer chez certains animaux domestiques. Ces variations étant généralement récessives, il est de toute probabilité que l'iris brun est dominant sur le clair-bleu-verdâtre.

Le rapport mutuel entre les gènes de ces trois caractéristiques dans notre arbre généalogique est assez difficile à établir clairement et il n'est pas facile non plus de présumer s'il s'agit du gène principal ou bien d'un modificateur éventuel car pour la dégénérescence pigmentaire et pour la couleur de l'iris par exemple, il existe différents moyens de transmission. Il est évident que les publications futures éventuelles au sujet de ces «linkages» ou de leurs pareils nous permettront de tirer des conclusions plus certaines.

Discussion

G. Meyer-Schwickerath (Bonn): Die Ausführungen von Dr. Nižetić haben mich sehr interessiert, da sie auch die Frage der Relation von Erbe und Umwelt berührt.

Im täglichen Sprachgebrauch ist Umwelt, was von außen auf das Individuum einwirkt. Für das Gen ist aber, streng genommen, schon der alle Partner «Umwelt». Darüber hinaus das Gennmilieu, d. h. die Summe aller Gene.

Ich glaube, daß viele schwer erklärbare Unregelmäßigkeiten im Erbgang auf die Wirkung der «inneren Umwelt» zurückzuführen sind. So muß der vorwiegende Befall weiblicher Personen mit einem bestimmten Merkmal nicht Ausdruck geschlechtsgebundener Vererbung sein, sondern es kann auch so sein, daß dieses Merkmal im weiblichen Gennmilieu bessere Manifestationsbedingungen findet. Vielleicht ist die Korrelation von Hornhautdystrophie und Irisfarbe, über die Herr Nižetić uns berichtete, darauf zurückzuführen, daß die Hornhautdystrophie nur in einem bestimmten Gennmilieu (welches phänotypisch an der Irisfarbe erkennbar ist) manifest wird.

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MIKROPHTHALMUS MIT DYSKRANIE UND DYSPHALANGIE

Von G. MEYER-SCHWICKERATH und E. GRÜTERICH

Der Mikrophthalmus ist bekanntermaßen oft kombiniert mit anderen Mißbildungen. Wir haben unsere eigenen Beobachtungen von Mikrophthalmus und die Fälle der Literatur daraufhin durchgesehen, ob sich bestimmte Syndrome herausstellen lassen, bei denen das konstante Zusammentreffen typischer Abweichungen eine zufällige Entstehung unwahrscheinlich macht.

Wir berichten zunächst über einen Typ vom Mikrophthalmus mit typischer Gesichtsbildung und Mißbildung des V. Fingers. Unser Fall ist ein 13 jähriges Mädchen mit Mikrophthalmus, einer eigentümlichen Physiognomie, wobei vor allem die kleine Nase mit nach vorn gerichteten Nasenlöchern auffällt. An den Händen befindet sich eine sehr kleine Mittelphalanx des 5. Strahls und an der linken Hand eine Abknickung der Endphalanx nach innen. Der Mikrophthalmus war in unserem Fall verbunden mit einem schwerregulierbaren Glaukom. Zu erwähnen ist noch, daß unser Fall Entwicklungsstörungen an den Zähnen in Form von Schmelzdefekten und eine auffällige Gelbfärbung aufweist. Außerdem fand sich Brüchigkeit der Nägel und der rostbraun verfärbten Haare, Symptome, die in den Rahmen der ektodermalen Syndrome gehören.

Zwei weitere Fälle, die dem unseren außerordentlich ähnlich sind, wurden 1920 von *Lohmann* publiziert. Auch hier finden sich wieder die merkwürdige Gesichtsbildung und die typische Mißbildung am kleinen Finger in einem Fall verbunden mit Schwimmhautbildung zwischen dem 4. und 5. Strahl. Die Ähnlichkeit aller drei Fälle ist so verblüffend, daß man die drei Mädchen für Geschwister halten könnte.

Vier weitere Fälle, die geringfügig von dem dargestellten Syndrom abweichen, finden sich in den Arbeiten von *Ciotola* und *Berliner*.

Ein zweites und wesentlich häufiger beobachtetes Syndrom wurde von *Ullrich* als Dycranio-pygo-phalangie bezeichnet. Da die eigene Beobachtung als besonders typisch gelten kann, soll sie zunächst berichtet werden.

Termingerecht wurde von gesunden Eltern, die nicht blutsverwandt sind und aus unbelasteten Familien stammen, ein 2620 g schwerer Junge geboren. Das lebensschwache Kind wurde gleich nach der Geburt in die Kinderklinik eingeliefert, dort wurden folgende Anomalien festgestellt:

Brachy- und akrocephaler Schädel mit vorspringender Stirn. Im Röntgenbild zeigte sich ein ausgesprochener Lückenschädel mit breitklaffenden Nähten und einer frontalen Encephalocoele, welche die vorspringende Stirn bedingt. Physiognomisch fallen grobe Gesichtszüge, eine eingesunkene breite Nasenwurzel sowie unterentwickelte Ohren mit eingekrempelem Muschelrand auf. Im Bereich der Lendenwirbelsäule findet sich eine Spina bifida aperta. Alle vier Extremitäten zeigen Hexadaktylie, wobei das 6. Glied der sonst normal gegliederten Extremität als kleines ulnares Anhängsel ohne knöcherne Verbindung gefunden wird. Außerdem fand sich eine Mikrognathie, Verschiebung der Haargrenze. Leistenhoden beiderseits mit Hodenhypoplasie. Nabelarterie, Urachusfistel und ein Colon mobile. Die Bulbi, welche eingehend histologisch von *Badtke* untersucht wurden, zeigten zusammenfassend folgenden Befund:

Mikrophthalmische Bulbi mit Mißbildungen der ektodermalen und mesodermalen Anteile, typische Netzhautkolobome, die das Bild des Bulbus septatus erzeugen: die Netzhautsepten stehen mit einer retrolentalen Gewebsplatte in Verbindung. Außerdem besteht eine fast komplette Aniridie, rudimentäre Anlage der Ciliarkörperfortsätze und Zeichen einer Dysgenesis Iridis et Corneae.

Als weitere Beispiele der Dycranio-pygo-phalangie möchte ich Ihnen die Fälle von *Ullrich*, *van Duyse*, *von Hippel* und *Gruber* erwähnen. Die letzteren dürften in dieser Reihe Extremfälle darstellen.

Wir haben also Mißbildungssyndrome vor uns, die darin übereinstimmen, daß gleichzeitig Mikrophthalmus, Gesichts- und Handmißbildungen vorkommen. Es ist vorstellbar, daß beiden Mißbildungstypen ein ähnliches teratogenetisches Prinzip zugrunde liegt, indem der gleiche entwicklungsgeschichtliche Ablauf etwa zur gleichen Zeit, aber in verschiedenem Ausmaß geschädigt wird, wobei beim ersten Typ die Merkmale wenig ausgeprägt, beim zweiten Typ so stark entwickelt sind, daß diese Individuen nicht mehr lebensfähig sind. Darüber hinaus kommt es beim Typ II noch zu zahlreichen Mißbildungen innerer Organe.

Im Fall der vorgestellten Mißbildungen spricht das bisher nur sporadische Vorkommen der Dycranio-pygo-phalangie für eine exogene

Ursache. Es muß allerdings bedacht werden, daß für den nicht lebensfähigen Typ eine Fortpflanzung nicht möglich ist. Was den lebensfähigen Typ angeht, so spricht die Beobachtung von *Berliner* über das Auftreten des Mißbildungssyndroms bei zwei Cousinsen I. Grades auch für die Möglichkeit einer erblichen Ursache.

Bei der Frage nach der kausalen Genese erscheint es mir nicht gerechtfertigt, eine alternative Entscheidung zu verlangen, ob es sich um eine erbliche oder umweltbedingte Abweichung handelt. Erbe und Umwelt sind schon am Beginn des Lebens so eng miteinander verflochten, daß der nachträgliche Versuch ihrer Trennung zwar als heuristisches Prinzip wertvoll ist, in Wirklichkeit aber oft eine Simplifikation bedeutet. Warum soll nicht durch das Zusammenwirken beider Faktoren eine zur Mißbildung führende Erkrankung der Frucht erst möglich werden? In der postnatalen Pathologie ist uns das Zusammenwirken von Erbe und Umwelt geläufig, aber auch in der pränatalen Pathologie können Begriffe wie Konstitution, Disposition und Diathese Gültigkeit haben.

Discussion

D. Klein (Geneva): I believe that the combination of colobomatous affections of the eye with hexadactyly and other malformations of the extremities must be classified among the atypical forms of Bardet-Biedl disease. In this syndrome one also finds very often anomalies of the uro-genital system and other organs. One case of atypical Bardet-Biedl disease, published by Dr. *Bornstein* of the Ophthalmological Clinic in Geneva (*J. Génét. hum.* 1, 211, 1952) showed aniridia with hexadactylia. The mode of inheritance was recessive as suggested by the consanguinity of the parents.

Edmund, J.: Acta genet. 7, 279-284, 1957

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BLEPHAROPHIMOSIS CONGENITA

By J. EDMUND

Among the numerous congenital developmental anomalies of the ocular adnexa, the congenital malformation of the eyelids in several respects form a particular group. In consequence of their location they are exceedingly disfiguring and in addition some of them hold a relatively

favorable position therapeutically. Both for these two reasons and also because of functional disabilities, the ophthalmologist is faced with strong therapeutic demands even very early in the patient's life.

It might seem obvious that the surgeon by marring malformations like these while using a relatively simple plastic-surgical procedure already in the early age, might be able to improve both the function and particularly the appearance. But in this respect both the patient and the surgeon are often disappointed.

One of the reasons for this disappointment is that in some certain malformations a special mode of reaction prevails depending on an interaction of a number of components each one in its own way obscuring the prognosis and impeding the therapy.

This is exactly what occurs in the syndrome of congenital blepharophimosis.

According to *von Ammon* the congenital blepharophimosis or phimosis palpebrarum is a general diminution of the palpebral aperture in all its dimensions, but with the lids themselves normally differentiated.

The deformity which I shall deal with in this paper, however, is not completely identical with the above, as the lids in my cases are not normally differentiated, but on the contrary incumbered with a combination of developmental anomalies complicating and impeding the therapeutic possibilities.

The object of the present study was partly to analyse the different clinical and pathological components in the malformation, partly by a study of the course and the reaction to surgical procedures to try to achieve the most appropriate operative procedure, and further, a very important factor, to decide at what time to begin surgical approach.

While the congenital ptosis though not common seems to be a relatively frequently occurring disease, the blepharophimosis congenita is exceedingly rare. Among 153 cases of ptosis of genetic origin admitted to the University Eye Clinic of Copenhagen since 1940 altogether only 12 cases of this rare disease were found. Detailed tracing of the hereditary cases brought up the total number to 23. Two families were found with a total of 15 affected individuals and 8 cases occurring as an isolated developmental anomaly. In the first family 7 cases were found out of 29 relatives in 4 generations. In the other family 8 cases were found out of 31 relatives in 5 generations.

Previous investigators, among others *Dimitry* in 1929 and *Waardenburg* in 1932, have described the clinical picture and explained the heredity by studies of single pedigrees. It is the question of congenital malformation

which might occur as an isolated developmental anomaly usually, however, with a strong hereditary predisposition as a rule being dominant and according to *Waardenburg* most often affecting males and generally with male conductor.

Although resembling ptosis the condition is essentially different, the lids being stretched over the orbital margins and constricted in their movements by the diminutive aperture and the tautness of their palpebral ligamentous attachments. The disease shows the following characteristics:

(1) a general diminution of the palpebral aperture, usually being from 10 to 15 mm. long and with a maximum separation from 2 to 4 mm. between the lids. This size remains constant through life. In certain instances in this material the palpebral fissure only altered some few millimeters during 25 years.

(2) Enlarged distance between the internal canthi. This distance often amounts to the double of the length of the palpebral fissure. This in connexion with

(3) the flat nasal bridge which gives the patient his very characteristic appearance.

(4) Immobility of the eyelids. This pseudo-ptosis, which is the most difficult point in surgical respect, is due partly to the above mentioned stretching of the skin over the underlying bony orbit partly to

(5) aplasia of the superior levator. On account of this there is no movement of the lids and

(6) lack of the tarsal fold.

The lid overhangs the corneae and covers the pupil. Compensatorily a continued over-action of the occipito-frontalis muscle throws the forehead into deep horizontal furrows and draws up the eyebrows into a highly convex arch. To aid improvement of vision the head is usually tilted back.

(7) The eyelids are defectively developed with thin, smooth, atrophic skin and rudimentary tarsal plate.

(8) Undeveloped eye-lashes, mostly reminiscent of lanugo-hair and located not in two or three rows along the edge of the lid but growing irregularly in a greater or lesser distance from the margo palpebrae especially on the upper lid.

(9) Dystopia or dislocatio laterovera of the puncta lacrymalia resulting in

(10) elongatio canaliculi lacrymalia. This anomaly contributes to

(11) the peculiar boat-shaped out-line of the palpebral aperture and

(12) the lack of contact between the bulb and the lids especially nasally resulting in epifora and giving the eyes a peculiar pseudo-phthisic appearance.

These are the proper characteristics. In addition the disease is often complicated with other defects, thus in both families mentioned in this paper a convergent strabismus; in many cases involvement of the superior rectus resulting in an insufficient upward movement of the eyes, latent nystagmus and one amblyopic eye. In addition, it may be accompanied by microphthalmus, anophthalmus, mongolism, dwarfism and oligophrenia. The three last mentioned possibilities occurring in case of consanguinity.

The complete and characteristic pathological picture is found almost only in hereditary cases as the isolated occurring instances, as it is often seen in all respects taking a milder course.

As mentioned it has been maintained by previous investigators that the heredity is dominant with mainly male transmission. The first pedigree confirms this theory.

A family with 4 generations is seen with the gene originating from a male in the first generation. In the second it appears in 2 males, but in the third generation it appears in 3 females and only one male. Out of the 3 females in the third generation 2 are minors. The third, an adult, has been sterilized. The male is unmarried. The 2 children in the fourth generation are normal. In this family the progress of the disease has been found to be far more pronounced in the 3 females than in the male and the reaction to operative approach has been disappointing. The male on the other hand has not been operated on and is much less disfigured by his anomaly than his 3 sisters. His vision is normal in both eyes without any squinting, unlike his 3 sisters who all suffer from convergent strabismus with amblyopia in the left eye. All family members of the second generation and their children were found to be normal.

The other family includes 31 members in 5 generations. The first and the second generation have not been examined but the anomaly, which is well recognizable, has been verified on pictures. In the third generation only one case is found in which the patient, though operated on several times, has only had less trouble from his defect. In the fourth generation 3 out of 7 members are affected, there being one female and 2 males. Once more, the affected female in this family has let herself be sterilized, while one of the male cases, who has descendants has transmitted the gene so that half of his children are affected. The other affected brother is unmarried and the off-spring of the unaffected members in the fourth generation are normal.

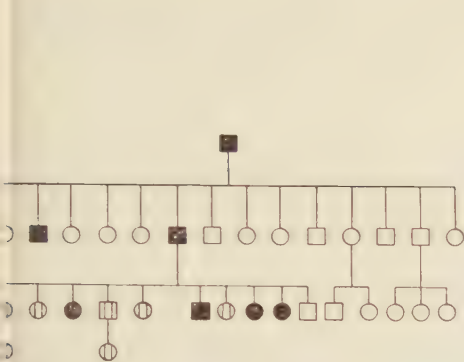


Fig. 1

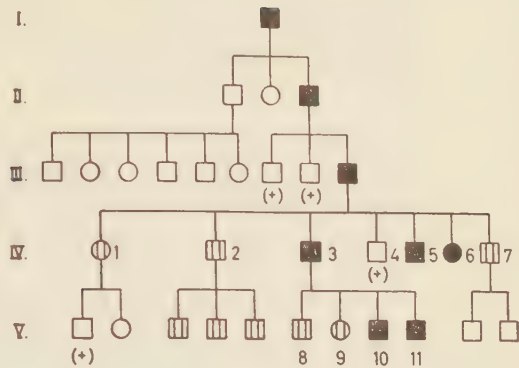


Fig. 2

It seems to appear from this pedigree that the first descendant oddly enough is never affected, but that the gene in all 4 generations omits the first and the second child but appears in the third.

It appears from both pedigrees that the trait is a dominant characteristic with male transmission, passing directly from affected person to affected person without any skips or breaks in the continuity. The exclusive male transmission in these families is unfortunately veiled by the fact that none of the affected females have bred any children. Further the sex-incidence is strange as affected females in the one family do not appear until the third generation and in the other not until the fourth generation. Though the sex-ratio thus seems almost equal a growing tendency to female manifestation appears in both families. Further the progress of the malformation seems to be much more pronounced in the affected females. In all cases the malformation is more severe in the off-spring than in the ancestor and the number of affected siblings also increase from generation to generation.

In no cases any combination with other congenital defects in other parts of the organism were found. Among the unaffected relatives no ocular anomalies of any kind were found.

Among the isolated cases the disease as mentioned in all instances show a more favourable course, partly showing a tendency to spontaneous improvement, partly a better reaction to operative procedures.

With regard to the therapy it has appeared from the operative results to be a matter of great difficulty. It is a question of repeated plastic-surgical procedures extended over several years, often complicated by considerable tendency to keloid formation and shrinkage of the tissues.

A detailed report of the operative technique and results is beyond the scope of this congress and will not be discussed on this occasion.

Discussion

A. Franceschetti (Geneva): Concerning the demonstrated cases of blepharophimosis I would like to ask Dr. *Waardenburg* about the relation between this affection and the syndrome described first by *van der Hoeve* under the name "elongatio canaliculorum inferiorum cum ankyloblepharon".

P. J. Waardenburg (Leiden): Blepharophimosis as a hereditary trait occurs in the following types:

(1) Blepharophimosis uncomplicata with deeply situated eyeballs as a dominant trait, rare in Europeans, more frequent in the Japanese. The lacrimal points are normally situated.

(2) Blepharophimosis as a correlated trait with microphthalmus and anophthalmus.

(3) Blepharophimosis combined with stiff ptosis. It arises in the 3rd embryonic month. Not only the *M. levator palpebrae* but also external ocular muscles may show disturbed function. The cause is not neurogenic but muscular maldevelopment combined with a shallow orbit and a flat face, and with an enlarged nosereach (intraocular distance) and laterally displaced lacrimal points.

(4) Blepharophimosis without ptosis, but with a dystopia laterovera of the inner angles and the lacrimal points. This affection is probably not an affection in itself, but a part of the syndrome, which may also present heterochromia iridum, a white hairlock and congenital deafness. It arises somewhat later in embryonic life than type 3.

Weekers, R., P. Moureau, J. Hacourt et A. André: Acta genet. 7, 284-287, 1957

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CONTRIBUTION A LA GENÈSE DES AMÉTROPIES PAR L'ÉTUDE DES JUMEAUX UNI ET BIVITELLINS

Par R. WEEKERS, P. MOUREAU, J. HACOURT et A. ANDRÉ

Cette étude a pour but de déterminer l'influence respective des facteurs génétiques, d'une part, et des facteurs exogènes, d'autre part, dans la pathogénie des amétropies. Elle est basée sur la comparaison des réfractions oculaires de jumeaux amétropes. Le caractère uni ou bivitellin

de ces jumeaux est établi *a)* par les membranes placentaires quand cet examen est possible, *b)* par les caractères de ressemblance, *c)* par la détermination des groupes et des facteurs sanguins selon la méthode de Penrose, employée par *Race* et *Sanger*. Ce dernier critère à lui seul, permet, en général, de déterminer le caractère d'uni ou de bivitellinité avec une probabilité supérieure à 80 %. Les trois critères précités, étudiés simultanément, nous ont permis d'arriver à une certitude presque absolue dans toutes les paires gemellaires qui constituent notre matériel d'étude.

Celles-ci sont au nombre de 27: 14 paires univitellines et 13 paires bivitellines.

Dans 13 paires univitellines et dans 13 paires bivitellines, l'amétropie est constituée par de l'hypermétropie ou de l'astigmatisme hypermétropique; dans une paire univitelline, par contre, l'amétropie est de la myopie.

Nous avons calculé en dioptries, pour chaque paire de jumeaux hypermétropes ou astigmatés hypermétropes, l'écart de réfraction entre les axes optiques des yeux correspondants. Nous avons additionné ces écarts, puis calculé l'écart moyen des 26 yeux de chaque série. Le tableau 1 donne les résultats de ces calculs.

Tableau 1. Etude comparative de la réfraction dans 13 paires de jumeaux univitellins hypermétropes ou astigmatés hypermétropes et dans 13 paires de jumeaux bivitellins hypermétropes ou astigmatés hypermétropes.

	Jumeaux univitellins	Jumeaux bivitellins
Ecart moyen (\bar{x})	0,894	3,202
Ecart type (S)	0,86	2,13

Le calcul statistique montre que les jumeaux bivitellins présentent un écart de réfraction considérablement plus accusé que les jumeaux univitellins. Cette différence est hautement significative ($p. > 0.0001$).

On doit en conclure *a)* que l'hypermétropie et l'astigmatisme hypermétropique résultent essentiellement de facteurs génétiques. Cette constatation confirme des travaux antérieurs de différents auteurs;

b) que l'identité d'une hypermétropie ou d'un astigmatisme hypermétropique chez deux jumeaux constitue un argument en faveur de l'univitellinité.

La paire de jumeaux univitellins myopes se comporte d'une façon très différente. L'écart entre les réfractions des yeux correspondants est considérable.

1er enfant	O.D. - 13 d. sph. = - 3,5 d. cyl. 75° O.G. - 13 d. sph. = - 3,0 d. cyl. 90°
2e enfant	O.D. - 8 d. sph. = - 3 d. cyl. 90° O.G. - 2 d. cyl. 90°

La comparaison des écarts des jumeaux univitellins hypermétropes d'une part et des jumeaux univitellins myopes d'autre part, confirme le comportement particulier de la myopie (tableau 2).

Tableau 2. Etude comparative de la réfraction des jumeaux univitellins hypermétropes et myopes.

Jumeaux univitellins hypermétropes	Jumeaux univitellins myopes	
Ecart moyen 0,894	Ecart entre les yeux droits 10,50	Ecart entre les yeux gauches 27

Quelles peuvent être les causes de la différence considérable du degré de myopie chez des jumeaux univitellins ?

Les faits d'observation aboutissent à des conclusions contradictoires.

a) Il existe dans certaines familles, un nombre élevé de myopes forts, constatation qui plaide pour l'importance d'un facteur génétique dans l'apparition et le développement de la myopie forte. Cette constatation rend, d'autre part, très surprenantes les discordances dans la myopie des jumeaux univitellins.

b) Certains myopies fortes ne sont certainement pas génétiques et sont dues à des facteurs péristasiques. Plusieurs observations en apportent la preuve.

Les yeux ayant souffert dans le jeune âge d'une affection grave et de longue durée (kératite phlycténulaire, par ex.) peuvent développer une myopie axile, progressive et grave. La prématurité, d'autre part, prédispose à la myopie.

La myopie des jumeaux univitellins décrite ci-dessus n'est-elle pas génétique ? L'hypothèse doit être envisagée. Ces enfants étaient vraisemblablement prématurés et pesaient respectivement à la naissance 2 kg. et 1,900 kg. Cette explication qui attribue aux facteurs péristasiques une importance prédominante n'explique cependant pas de façon satisfaisante la discordance des myopies puisque les deux enfants ont toujours vécu ensemble et ont été soumis aux mêmes influences extérieures.

c) Une troisième éventualité serait que la prédisposition à la myopie est génétique, mais que le développement de cette amétropie peut atteindre un degré variable sous l'influence de facteurs inconnus.

Cette brève note, dépourvue de bibliographie, est le résumé d'un travail qui paraîtra, *in extenso*, dans les Archives d'Ophthalmologie.

Discussion

A. Franceschetti (Geneva): La manifestation souvent discordante de la myopie pathologique chez les jumeaux univitellins parle en faveur d'un gène labile. La question est d'autant plus complexe que la fibroplasie rétrocrystallinienne, la toxoplasmose oculaire congénitale, ainsi que d'autres embryopathies, peuvent être responsables de l'apparition d'une myopie congénitale.

Waaardenburg, P. J.: Acta genet. 7, 287-290, 1957

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DIFFERENT TYPES OF HEREDITARY OPTIC ATROPHY

By P. J. WAARDENBURG

Hereditary optic atrophy can arise at different ages. It should be distinguished from the very rare optic aplasia, where the nerve fibres of the ganglion cell layer of the retina fail to grow into the optic stalk. The region of the disc is not white in these cases as it is in optic atrophy. We may distinguish the following clinical and genetical types according to the age of onset:

(1) A rare and serious *autosomally recessive* optic atrophy that may be either connatal or may have developed early postnatally in a hitherto unknown way. We must assume that optic fibres have existed for a short time but that they have again degenerated by some abiotrophic process. Nystagmus is usually present. *Nettleship* [1890] described 3 affected siblings, 2 of whom showed a slight skull anomaly with normal intellect.

A possible variant of this type is an optic atrophy which I found in 3 siblings with consanguineous parents, as a part of an incomplete connatal achromatopsia. It may be compared with the ascending optic atrophy in infantile amaurotic idiocy, in some cases of macular dystrophy, in dystrophia retinae pigmentosa and in luetic fundus affections. It is likely that still another *late infantile* recessive type exists (*Apple* with age of onset 9 and 7 years; *Favory* and *Petriguani*: onset 11 years in a consanguineous marriage with a probably secondary achromatopsia in 2 of the 3 affected brothers).

(2) The *autosomal-dominant early infantile* or probably also connatal chiefly *stationary optic atrophy*. The affected persons cannot remember a time of onset (earliest case in literature 2 years. Cases are described where the anomaly seemed to arise in infancy). Subdivision:

(a) The type of *Riedl*, *Graham Scott*, *Jaeger* and *Kjer* with a preponderant disturbance of the blue-yellow sensation showing reserved colour-fields: blue within red and the red as the only still recognized colour in more progressive cases. It offers a rather good prognosis. It is still doubtful whether these receptors are the primary seat of the dystrophy. There is no hemeralopia. Most of the affected persons are self supporting and some of them have not even noticed, that they have the affection.

(b) *Other dominant types* without special disturbance of the blue sense. The modification range is here generally greater. Severe cases may alternate with slight cases in the same family. I encountered a Dutch family where all affected people became blind in infancy. The prognosis is generally not the same for all family members, there may be cases with a rapid progression, leading to nearly total blindness. The origin is unknown. I stress the point that in my opinion this anomaly comprises various biotypes, which we will have to differentiate in future.

(c) The *infantile recessive* type complicated with symptoms of the nervous system as increased tendon reflexes, disturbances of coordination (ataxia) and incontinency of the bladder (type of *Behr*). Possibly this type may often be a connatal one. The cells of origin of this affection are unknown. Abortive and atypical cases seem to occur. Late infantile cases are also mentioned (*Hermann* and *Freudenthal* [1933] in a consanguineous marriage, *Kreuzeder* [1938]).

(d) The optic atrophy (*type of Leber*) mostly developing in an acute way between 12 and 30 years.

In contradistinction to the other types mentioned, this disease affects chiefly male persons in the people of European descent. In the Japanese,

many more females are affected than in the people of white descent. In many cases a prechiasmatic arachnoiditis has been found, so that the affection could be cured by early surgical treatment.

In the beginning, the mode of inheritance was assumed to be an X-chromosomal one. This explained the normal sons of affected males, but not the normal grandsons by daughters of affected males, and the fact that all daughters of affected males are normal contrary to those of affected or conductor females. I proposed an auxiliary cytoplasmatic hypothesis. The other autosomal hypothesis (Japanese authors, *Ruth Lundsgaard*) want an auxiliary hypothesis as well. It is here assumed that the gene for Leber's disease has a lethal effect on the tainted spermatozoa, but not on the egg cells of manifest or a latent female conductor and that a different predilection of manifestation exists in both sexes. The mode of inheritance is not yet clear. X-chromosomal inheritance may be excluded if it should never be linked with other X-chromosomal traits.

(e) Hereditary optic atrophy may be a *symptom of hereditary affection of the nervous system*, not only in *Behr's* atrophy but also in other syndromes, e.g. an infantile optic atrophy may be combined with a recessive familial spasmodic *paraplegia or cerebral diplegia* and strabism (*Freud, Borel*). I saw one case of that type in one of dizygotic male twins. It may further be part of *Charcot-Marie's neural atrophy* (rarely) with pupillary trouble, *Krabbe's infantile cerebral sclerosis* (rare), *Tay Sachs' infantile amaurotic idiocy*, *Unverricht's familial myoclonia* (1933). It has been found in *Friedreich's* and in *P. Marie's* ataxia. In cerebellar ataxia, optic atrophy may already occur in early stages of the disease whereas in spinal ataxia it more often occurs in the end stages. *Sjögren* found optic atrophy in 13 per cent (9 of 68) of his *Friedreich* cases and in 48 per cent (11 of 23) of his *P. Marie* cases.

(f) Optic atrophy as *complication of hereditary skeletal anomalies*, e.g. in osteopetrosis of *Albers-Schönberg* or in types of craniostenosis.

Discussion

A. Franceschetti (Geneva): Concerning the interesting paper of Dr. *Waardenburg*, I would like to stress the fact that electroretinography (ERG) has become of great importance for the differential diagnosis of ascending and descending optic atrophy. Indeed, in the former the electric response is in general diminished or extinguished, whereas in the latter the b-wave is normal or even increased. We have been able to confirm that in infantile amaurotic idiocy (*Tay-Sachs*) the ERG remains normal till death; so we can conclude that the atrophy is descending. It is probable that many cases of infantile optic atrophy mentioned in the literature are in fact tapeto-retinal degenerations without typical fundus

alterations. Indeed, during the last 3 years we have been able to discover thanks to the ERG not less than 8 cases of Leber's infantile tapeto-retinal amaurosis.

I quite agree with *Waardenburg* that the infantile complicated optic atrophy of Behr is not so rare as we generally think. However, the neurological symptomatology is not always the classical one. We have observed two cases with sequelae of hemiplegia.

W. Jaeger (Heidelberg): Die Ergebnisse der Farbennuntersuchung mit Schwellenwertbestimmungen hängen sehr davon ab, welche Farbpapiere man benützt. Bei den Engelking-Eksteinschen Papieren, die wir verwendeten, ist das Blau verhältnismäßig ungesättigt. Ist es möglich, daß bei den Untersuchungen von Dr. *Waardenburg* die Inversion der Farbgrenzen vielleicht deshalb nicht gefunden wurde, weil das Blau zu gesättigt war?

Ein charakteristischer Zug im Verhalten der Patienten mit dominanter Optikusatrophie verdient noch besondere Erwähnung: Selbst bei schon erheblich herabgesetztem Visus sind die Patienten subjektiv noch verhältnismäßig wenig behindert. Ich selbst habe mich von einem der Patienten (Visus 5/35 jds.) in seinem Volkswagen auf dem Land herumfahren lassen, um seine Verwandten zu besuchen. Ich war ganz erstaunt, wie sicher er fuhr. Diese verhältnismäßig geringen subjektiven Beschwerden sind vielleicht der Grund, weshalb von den leichteren Fällen von dominanter Opticusatrophie so viele bisher der Beobachtung überhaupt entgangen sind.

Kjer, P.: Acta genet. 7, 290-291, 1957

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HEREDITARY INFANTILE OPTIC ATROPHY WITH DOMINANT TRANSMISSION

By P. KJER

On the basis of an investigation of 20 Danish families with about 250 affected members with optic atrophy a clinical picture—absolutely different from that of Leber's disease—is described.

It is characteristic for the disease that it begins unnoticed in early childhood, so that the weak sight is as a rule first discovered at the beginning of school attendance. In less serious cases the disease remains unnoticed.

The visual acuity varies within a wide range from normal to considerably decreased vision. Besides optic atrophy there was only slight or no alterations at all in the macula.

Examination of the visual field showed either isolated, temporal, para-central scotoma or scotoma merging into the blind spot, so that this apparently was enlarged, possibly reaching the centre or occupying the whole central part of the upper or lower temporal quadrant.

Colour vision showed characteristic defects especially in the perception of blue.

There was no nystagmus and the transmission was dominant autosomal.

The paper has been published in Danish Medical Bulletin 3, 135-141, 1956.

Discussion

W. Jaeger (Heidelberg): Der genaue Zeitpunkt des Auftretens der Opticusatrophie bei dominanter Opticusatrophie ist immer noch nicht bewiesen. Es wäre deshalb wichtig, zu wissen, ob es Dr. Kjer einmal in seinen zahlreichen Fällen gelungen ist, ein Kind mit normaler Papille zu sehen, das später nachweislich eine Opticusatrophie bekommen hat. In meinem Material ist einmal von einem Augenarzt zwischen dem 4. und 5. Lebensjahr das Auftreten einer Opticusatrophie beobachtet worden. Ich selbst habe darüber noch keine Beobachtungen gemacht.

Ich stimme ganz mit Dr. Kjer darin überein, wenn auch ich glaube, daß die dominant vererbte Opticusatrophie wesentlich häufiger vorkommt, als wir das noch vor wenigen Jahren annahmen.

A. Franceschetti (Geneva): As in cases of dominant retinitis pigmentosa, also in dominant infantile optic atrophy all children of affected parents should be examined systematically since birth. We should not forget that the electroretinography gives significant responses already 6 months after birth.

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SOME DOMINANTLY INHERITED CENTRAL FUNDUS LESIONS

By ARNOLD SORSBY

Seven affections inherited in a dominant manner, each showing a central fundus lesion, are now known. Two of these affections are congenital and five abiotrophic in character.

(1) Congenital anomalies

(a) *Congenital macular coloboma*. Several pedigrees of dominant inheritance of macular coloboma are now available. There is as yet only one pedigree in which associated skeletal defects of the brachypharyngeal type were present. Ophthalmoscopically these colobomata show considerable pigmentary disturbances and vision is sometimes surprisingly good, such as 6/24.

(b) *Macular cysts*. This, too, is a congenital anomaly and it is possible that what is known as Best's disease is a variant of this affection, for the cysts vary considerably in size as between different families, but not intra-familially. Vision remains good as long as the cyst is intact. Only when the cysts burst do degenerative changes set in, shown by fine pigmentary reaction around the burst cyst. In some patients it is easy to see ophthalmoscopically that the lesion is indeed cystic in character, either before it has burst or subsequently. In most cases there is a deceptive appearance of a hole at the macula.

It is noteworthy that, though both these lesions are congenital, macular coloboma is a stationary and macular cyst a progressive affection.

(2) *Abiotrophic defects*

(a) *Central areolar choroidal sclerosis*. This affection was known to *Liebreich* and was fairly fully described by *Nettleship* in 1884 under the term central senile areolar choroidal atrophy. The lesion is not senile in character and only indirectly an atrophy. Onset is at about the age of 20, giving the appearances of a macular dystrophy. There is slow deterioration over the years and the characteristic ophthalmoscopic picture develops at about the age of fifty. The affection is generally recessive, but two families with dominant inheritance are known. The end result is a loss of central vision but no extension peripherally.

(b) *Macular dystrophy*. In contrast to recessive macular dystrophy of the Stargardt type, dominant macular dystrophy is not well known, though there are many records in the literature showing dominant inheritance. The characteristic features of the affection are:

- (1) onset in adult life;
- (2) unusual colour anomalies, either before ophthalmoscopic features develop or in the early stages of the ophthalmoscopic picture;
- (3) central vision remains good until about middle life;
- (4) the lesion is steadily progressive, and finishes in old age as one of the forms of senile macular degeneration.

(c) *Doyne's dystrophy*. This affection—also known as *Maladie Leventinese*—is not particularly rare, and constitutes a clear clinical entity with the following features:

- (1) the early signs are present probably by about the age of 20;
- (2) in many cases the condition remains clinically silent, even if there is a well developed ophthalmoscopic lesion;
- (3) ophthalmoscopically the affection shows itself by colloid bodies on the nasal edge of the disc, as well as the patterned colloid body reaction seen centrally. In well marked cases, streak-like pigment is a characteristic feature in the central areas;
- (4) the periphery is not invaded to any extent.

Doyne's dystrophy must be regarded as essentially a mild affection, for generally it does not go on to a substantial loss of central vision.

(d) *Generalized choroidal sclerosis*. The early stages of generalized choroidal sclerosis suggest a macular dystrophy. It probably occurs in childhood and is slowly progressive; vision remains good until about the age of 30, or later, when the nature of the affection is seen from a central choroidal sclerosis becoming apparent and spreading towards the periphery. The end

stage is conversion of the choroidal vessels into white streaks all over the fundus.

(e) *Generalized fundus dystrophy*. This shows the following features: The affection generally begins at about the age of 40 years and takes some 35 years to run to its end stages. The first subjective symptoms are blurring of central vision in one eye followed by the same symptoms in the other eye, generally within a matter of months but occasionally simultaneously or not for a few years. Central vision rapidly declines, but there is no involvement of peripheral vision or colour vision at this stage.

Objectively, the first signs are oedema, haemorrhages and exudates in the central area. This progresses to scar formation with a varying amount of pigment proliferation, which may be exceedingly massive. The choroidal vessels become exposed and show some sclerosis. Over the course of years the process extends peripherally, choroidal sclerosis generally becomes more manifest and sometimes dominates the picture. The end-stage is widespread disappearance of the choroidal vessels exposing the sclerotic covered irregularly by proliferating pigment; at this stage there is practically total blindness.

Differential diagnosis

Congenital macular coloboma and macular cyst represent no difficulties in diagnosis. Central areolar choroidal sclerosis, macular dystrophy, and generalized choroidal sclerosis may all begin as fairly similar lesions, suggestive of a macular dystrophy. Whilst macular dystrophy may go on to an extensive macular scar simulating "senile" macular degeneration, central areolar choroidal sclerosis develops into an unmistakable picture, and generalized choroidal sclerosis progresses to become an extensive lesion also with unmistakable features. Doyne's dystrophy is easily diagnosed by the patterned reaction centrally, and the streaky pigment lines, and by the tell-tale colloid bodies on the nasal edge of the disc.

Generalized fundus dystrophy is polymorphic, and the different stages of the affection can easily be mistaken for several varieties of fundus disturbances—the early stages for a macular oedema of haemorrhagic or metabolic origin, the intermediate stages for inflammatory affections, and the end stages for the late stages of choroideremia.

The value of accurate diagnosis is considerable, as the prognosis in Doyne's dystrophy is relatively good, and the prognosis is also fairly good for macular dystrophy, central areolar choroidal sclerosis and for macular cyst. The poorest prognosis is for generalized fundus dystrophy. Irregular

dominance may occur in macular cyst; it has not been observed in the remaining affections.

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Discussion

A. Franceschetti (Geneva): I have been especially impressed by the extensive pigmentation of the hereditary macular colobomas showed by Prof. Sorsby. Although it is not probable that these familial cases are due to toxoplasmosis, it nevertheless would be interesting to know the results of the serological reactions. The dominant macular degeneration can also already appear in the earliest childhood (see Franceschetti, A., and coll.: Bericht Dtsch. Ophth. Ges. Heidelberg 59, 66-71, 1955). Concerning the generalized fundus dystrophy described by Sorsby I would suggest to call it presenile generalized fundus dystrophy, in order to distinguish it clearly from other infantile and juvenile diffuse tapeto-retinal degenerations.

P. J. Waardenburg (Leiden): At what age was the onset of your cases of cystic macular dystrophy?

We found in the Netherlands three families where the siblings showed the affection already in their youth. In one of these families the cyst was replaced after some time by an ordinary macular dystrophy and only from that time was the vision impaired.

A. Sorsby (London): In reply to Waardenburg: As to macular cysts, they generally break down at about 40, but in one of the five families studied two children had trouble at 9 and 10 years of age.

In reply to Franceschetti: Stargardt's original paper describes what must be considered retrospectively as several distinct entities. It is worth while keeping the recessive, acute lesion setting in at puberty,—the genuine Stargardt's Disease—distinct from the dominant type discussed this afternoon.

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A STUDY OF RETINOBLASTOMA IN OHIO FAMILIES

By M. T. MACKLIN

An attempt has been made to obtain the names of all children born in Ohio since 1940 on whom diagnosis of retinoblastoma has been made. Sixty-three such families have been contacted in whom there is a history of sibs born before and after the affected child. In two families, a parent was affected; 5 or 8% of the total had sibs affected, with normal parents; 5 had other relatives affected. Twenty-eight patients were the last in the family, so that there was no opportunity of judging whether subsequent children might be affected. Ten patients who were the last in the family were ten years or more old; one was 9 years old, and four were 7. They probably would not be followed by any further sibs. Of the 35 sets of normal parents who did have children after the birth of the retinoblastoma patient, 5 or 14.2% had other affected children: 2 had one more affected, and one family each had 2, 3, and 5 more affected. Of the 97 children born in these families after the child with retinoblastoma, 13 or 13.4% had the disease also.

Discussion

A. Franceschetti (Geneva): We must be very thankful to Mrs. Macklin for her interesting survey on retinoblastoma families. Years ago we have stressed the fact that in familial cases of retinoblastoma the frequency of affected siblings calculated by Weinberg's method is about 40% (*Franceschetti, A.*: Kurzes Hdb. d. Ophth., J. Springer, Berlin 1930, Vol. 1, p. 715; *Franceschetti, A.*, and *V. Bischler*: Arch. Julius-Klaus-Stiftung 21, 322, 1946).

According to *Dollfus* (Rapp. Soc. franç. Opht. 1953, p. 37) only 1 to 2% of the children born after the birth of a retinoblastoma patient with normal parents are again affected. Although Mrs. Macklin found 13.4% of other affected children, there is a great difference between this frequency and that in retinoblastoma families mentioned above. I have

suggested that this difference may be due to the fact that in "isolated cases" the mutation occurs not in the parental genome, but in the germinative cells of the future patient or even afterwards in the course of development (Bull. Mém. Soc. franç. Opht. 66, 21, 1953). What is speaking in favour of that theory is the high frequency of affected children, if one of the parents has had a retinoblastoma. Also Mrs. Macklin found in the two families, where a parent was affected, affected children again. It seems therefore that also in apparently "isolated cases" the retinoblastoma is transmitted as a dominant trait with a penetrance of about 80% (*Franceschetti, A and V. Bischler, 1946; Franceschetti, A., 1953, loc. cit.*).

Alström, C.-H.: Acta genet. 7, 297-298, 1957

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A PRELIMINARY REPORT ON AN INVESTIGATION OF A MONOHYBRID, AUTOSOMAL, RECESSIVE FORM OF CONGENITAL RETINO-CHOROIDIT

By C.-H. ALSTRÖM

About 10 per cent of the pupils admitted to Tomtebodas Institute for the Blind—the central institution for the education and registration of mentally healthy blind children in Sweden—suffer from a congenital form of retino-choroiditis. Fundus changes are described, early in life they are sparse or even absent. Later complications are cataract and keratoconus. ERG findings are reported. Papers by Leber 1869-1871 are mentioned. The cases show a tendency to familial incidence and a high degree of relationship between the healthy parents. Altogether 105 families of which about $\frac{1}{4}$ belong to 6 larger family-complexes have been investigated. The clinical part of the investigation was performed in collaboration with the ophthalmologist at Tomteboda, Dr. O. Olson. The manifestation of the trait seems to be complete. The frequency of those affected in the sibships was calculated according to Haldane's method to be 0.274 ± 0.025 . The frequency of first cousin relationship among the parents was 0.162 ± 0.036 . The mean coefficient of inbreeding was 0.01. The frequency of affected "recessives" in the population was estimated to

be about 0.00 00 3. The trait is spread throughout the whole country, but with different frequencies. The disease is called Heredo-Retinopathia Congenitalis.

Discussion

A. Franceschetti (Geneva): The large pedigree examined by Dr. *Alström* is of greatest interest. Without seeing a picture of the fundus it is naturally too difficult to say to which group of congenital tapeto-retinal affection this trait belongs. It would certainly be preferable to speak of congenital retinal choroidosis or congenital chorioretinopathia. Recently *Appelmans* and *Michiels* (Soc. Franç. Opht. 1956) have described a curious diffuse congenital affection of the retina having a gliomatous appearance. Together with Dr. *Forni* we have recently observed a child of 2½ years (*D. Silverio*: obs. clin. 12466) with a curious white net formation in the whole peripheral retina. The ERG was completely abolished. The parents of the father were first cousins.

P. J. Waardenburg (Leiden): In the Netherlands we found many cases of congenital blindness with absence of pupillary reflexes in children, some of whom were siblings, in asylums for the blind. We now try systematically to establish an ERG. In our experience, it was always absent. We could not find any definite affection of the retina nor of the optic nerve to explain the blindness. In some juvenile and adult cases we have found some pigmentary anomalies of the fundus. Our findings resemble those of *Leber* when he was consultant oculist to a blind-asylum, but we have not as yet found cases with congenital cataract. Only in one or two families cataract arose as a later complication. But what we found in several, also familial cases, was the combination with keratoglobus. We think therefore that this combination is a special entity.

Ohrt, V.: Acta genet. 7, 298-301, 1957

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OCULAR ALBINISM WITH CHANGES TYPICAL OF CONDUCTORS IN A DANISH FAMILY

By V. OHRT

Ocular albinism is a form of incomplete albinism in which the lack of pigment is chiefly confined to the eyes. The condition is relatively rare, but since it was described for the first time by *Nettleship* in 1909, it has been demonstrated in several families.

I wish to present yet another family with the disorder, due to the fact that recent observations have thrown new light on the character of the disease-producing gene. *Nettleship* was aware that this gene was sex-linked, but assumed that it was recessive. However, although this assumption prevailed for several years, it does not hold; recent investigations have proved that the sex-linked gene of the affection is intermediate in its expression.

The ocular symptoms encountered in males with ocular albinism are also well known in generalized albinism. Affected individuals suffer from impaired vision and undulatory nystagmus; the retinae are poor in pigment; the choroidal vessels are seen with great clearness, and the macular areas are hypoplastic, lacking the yellow colouration normally seen in red-free light. The irides are bright and translucent, so that the pupil may appear faintly red. Strabismus and astigmatism are usually present. In addition, head nodding is often seen in early childhood.

Attention has particularly been focussed on this complex of characteristic symptoms in the males, whereas little interest has been taken in the apparently unaffected females.

However, in 1947, *Waardenburg* found that it was possible to reveal that these heterozygous females were carriers, as their irides also showed translucency. A few years later, in 1951, *Falls* established what had been rendered likely by *Waardenburg*'s observations, viz. that ocular albinism has an intermediate sex-linked mode of inheritance; he described a peculiar ophthalmoscopic picture which he had observed in all female carriers in two American families in which male members exhibited ocular albinism.

François and *Deweert* have later described a large Belgian family of 179 members who exhibited exactly the same changes as had previously been observed by *Falls*.

I have had the opportunity of studying a Danish family consisting of seven generations with 169 members. Of these, 81 individuals representing four generations were examined personally. Five males, including a pair of monozygotic twins in whom the affection showed pronounced parallelism, revealed ocular albinism. In addition, unquestionable information of the disease was available in three men who had died. Of the females, 14 exhibited the changes described by *Falls* to be typical of carriers.

Ophthalmoscopically, the eyeground of such a heterozygous female reveals normal pigmentation in the central area. The macula has retained its reflexes, but it is often denser and coarser in its pigmentation than normal. Peripherally, a peculiar, polymorphous pattern of greyish brown, irregular patches of granular pigmentation is seen. They begin centrally

as weak granules, occasionally deposited as small rings; towards the periphery they increase in size, become more confluent, maplike, mainly radially arranged, and are separated by areas poor in pigment and with clearly visible choroidal vessels.

This picture was observed in all 14 conductors; it is characteristic and easily recognizable, but there were variations with regard to the intensity of the pigmentation and the relation between the areas with and without pigment deposits. In this respect, two individuals differed from the others, viz. the mother of the aforementioned identical twins and the elder of her two daughters, who were both heterozygous. In these two, the areas with sparse pigmentation were larger, the patches of pigment smaller and weaker than in the others and thus, although typical of carrier eyegrounds, more like the retinae of the affected males. In the other conductors the variations were small, but it seemed to be the rule that in individuals with dark skin and hair the patches of pigment were somewhat denser and darker than in those of a lighter colour.

Other findings of interest were revealed in these carriers. The mother and her daughter revealed a periodical, fine undulatory nystagmus—rarely present in the darker mother, but frequently seen in her blond daughter. Another blond, heterozygous woman had a similar nystagmus. This woman suffered from visual impairment in both eyes (6/12), fairly pronounced nystagmus and slight convergent strabismus. Her darker sister had slight divergent strabismus, astigmatism of almost the same intensity, but a visual acuity of 6/9 in both eyes and no nystagmus. Astigmatism and strabismus were also present in other carriers; in one case together, in the others isolated.

Of 11 carriers studied for translucency of the irides, nine showed this symptom, while it was absent in two dark-haired women.

In the first place, these findings show that female carriers may exhibit abortive symptoms of ocular albinism other than the ophthalmoscopic changes, which are constantly present, and the diaphaneity of the irides, which is usually, but not invariably, present.

Secondly, the investigations show that there must be a considerable variation in the expressivity of the intermediate gene. Previous investigations may be interpreted in the same direction. Thus, for example, in the paper of *François and Deweer*, it is stated that three of an affected man's five daughters had normal eyegrounds, but as neither this nor previous studies leave doubt as to a sex-linked mode of inheritance, these three women must have been carriers, and the expressivity of the gene must, accordingly, have been very weak. The same was the case with one

of *Falls'* patients, a one-eyed man with very mild ocular albinism; the visual acuity was normal and the eyeground revealed patches of pigment of an appearance as in heterozygous women.

When information is given as to the general pigmentation of affected males in the literature on this disorder, these individuals are usually described as blond, sometimes as white-haired and with a fair complexion. This suggests that the responsible gene has a wider effect and, as emphasized by *Sorsby*, may produce mild manifestations of generalized albinism. In the family I studied, information was available as to the general pigmentation in seven of the eight males. Of these, six belonged to the blond type, and it was characteristic of most of them that in childhood they had had almost white hair and had been unable to become sunburnt. The pigmentation increased with age; although they remained blond in adult life, they were not strikingly fair, and they were able to become tanned by the sun to some extent. One of the deceased males—the son of very dark parents—with unquestionable impairment of vision and nystagmus had been dark. This variation should presumably also be seen on the background of the expressivity of the gene.

The general pigmentation varied within wide limits in the carriers. On the whole, most abortive symptoms were present in the blondes and seemed often most pronounced in these, even though those with dark hair also sometimes showed considerable affection. It is therefore reasonable to assume that the gene is also able to exert a certain, although weak, influence on the general pigmentation in carriers.

The conclusion must be drawn that the sex-linked intermediate gene which is responsible for ocular albinism shows considerable variability with regard to expressivity, and that in addition to the principal effect on the eyes, it also has a weak influence on the general pigmentation.

Discussion

P. J. Waardenburg (Leiden): I am, of course, much interested in this pedigree because we found in Holland in a very large family stock only one exception to the rule that daughters of affected males could be recognized either by a diaphanic iris or by peripheral fundus alterations. Now you said you thought there was a rather large variability among the daughters and to make your assumption acceptable you said that *François* and *Deweert* had also found negative cases among the daughters of affected males. My co-operator *Van den Bosch* has been able to visit Prof. *François* and to re-examine those so-called negative females. He was able to demonstrate to Prof. *François* who has admitted it, that the negative females were also positive, so that it seems to be a question of the method used. Split lamp illumination e.g. is not suitable for this purpose.

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ON EUGENIC PROBLEMS IN PREVENTION OF BLINDNESS

By H. SKYDSGAARD

It is well known that the causes of blindness in certain areas of the world have changed, as infectious conditions have steadily decreased, whilst simultaneously a percentage increase has been registered in those groups comprising congenital and hereditary conditions.

Eugenic measures have thus become more and more important for the prophylaxis of blindness. Such measures include providing eugenic information to the persons concerned regarding their present condition and contraceptive instruction, artificial abortion, and possibly sterilization.

The paper gives a survey of the experience gained from eugenic work in the ophthalmic clinic of "The Royal Institute for the Blind" in Copenhagen.

The paper will be published in extenso in *Acta Ophthalmologica* 1957.

Tuttlingen, Württemberg, Deutschland

NEUE ERGEBNISSE DER GENETIK DER MUSKELDYSTROPHIEN *

Von P. E. BECKER

In den letzten Jahren sind mehrere bedeutende Untersuchungen veröffentlicht worden, die zur Klärung der genetischen Verhältnisse bei den Muskeldystrophien beigetragen haben.

Die «Dystrophia musculorum progressiva», die *Wilhelm Erb* als eine klinische Einheit aufgefaßt hat, setzt sich aus 4 verschiedenen genetischen Typen zusammen. Hinzu kommt dann noch die sogenannte «distale Form», die Frau *Welander* sorgfältig untersucht hat und die sogenannte «oculäre Muskeldystrophie», deren Erblichkeitsverhältnisse noch nicht geklärt sind; beide bleiben hier außer Betracht.

Am häufigsten ist ein x-chromosomaler Typ. Er wurde von *Tyler* und *Wintrobe* [1950] sowie *Stephens* und *Tyler* [1951] als "childhood progressive muscular dystrophy" bezeichnet und von *Stephenson* [1953], der ebenfalls eine umfangreiche genetische Untersuchung durchgeführt hat, als «Duchenne type rapidly progressive muscular dystrophy of young boys» genannt. *Walton* und *Nattrass* [1954] und *Walton* [1955] bezeichnen diese Muskeldystrophie in ihrer sehr sorgfältigen Untersuchung als «Duchenne type», während *Hanhart* [1950] sowie *Lamy* und *Gronchy* [1954] es vorziehen, einfach von x-chromosomaler Muskeldystrophie zu sprechen. Ich selbst habe in den Jahren 1939-1941 in Baden 26 Sippen untersucht mit insgesamt 60 Kranken, die wahrscheinlich zu diesem x-chromosomalen Typ gehören. Die Kranken sind männlichen Geschlechts und, wenn sie in mehr als einer Geschwisterreihe vorkommen, über die Mütter miteinander verwandt, die Eltern sind regelmäßig gesund. Die theoretische Wahrscheinlichkeit zu erkranken, beträgt für die männlichen Geschwister 50 %, er-

* Herrn Prof. Frhrn. v. *Verschuier* zum 60. Geburtstag gewidmet.

rechnet wurden $41 \pm 6,8\%$ in den Geschwisterreihen, die über die Probandengeschwisterreihen erfaßt worden sind. In der klinischen Kennzeichnung stimmen alle genannten Untersucher überein: Das Leiden beginnt innerhalb der ersten 3 Lebensjahre mit Schwäche der Oberschenkel- und Beckengürtelmuskulatur, Pseudohypertrophie ist regelmäßig vorhanden, die Rumpf- und Schultergürtelmuskulatur ist sehr bald, spätestens 3–6 Jahre nach Beginn, ebenfalls betroffen. Um das 12. Jahr werden die Kranken regelmäßig gehunfähig, und der Tod tritt spätestens in der ersten Hälfte des 3. Lebensjahrzehnts ein. Die Bezeichnung Muskeldystrophie ist eigentlich unvollständig, da außer der Muskulatur auch das Fettgewebe und das Skelett einem dystrophischen Prozeß verfallen. Der Herzmuskel ist häufig mitbetroffen. Die Teste sind vielfach abnorm klein oder der Descensus ist unterblieben. Schwachsinn kommt vermutlich überdurchschnittlich häufig vor. Kein Kranker hat Nachkommen. Die Ausmerzungsrates ist also hoch, deshalb ist auch die Mutationsrate beträchtlich. Für Südbaden haben *Lenz* und ich sie mit der direkten Methode auf $3,2 \cdot 10^{-5}$ geschätzt und mit der indirekten Methode auf $4,8 \cdot 10^{-5}$, dieser Wert ist mit dem der direkten Methode innerhalb des Fehlers der kleinen Zahl von $1,6 \cdot 10^{-5}$ vereinbart. *Walton* schätzte die Mutationsrate in Northumberland und Durham auf $4,3 \cdot 10^{-5}$, *Stephenson* in Nordirland auf $6,47 \cdot 10^{-5}$ und *Stephens* und *Tyler* im Staate Utah auf $9,5 \cdot 10^{-5}$. Es besteht eine gute Übereinstimmung der Schätzungswerte der Mutationsrate in den verschiedenen Ländern.

Vieles spricht dafür, daß es noch eine weitere x-chromosomale Muskeldystrophie gibt. *Walton* [1955] war es aufgefallen, daß in einer seiner x-chromosomalen Sippen (D 6) die Muskeldystrophie bei allen 6 Kranken spät begonnen hat und langsamer, mehr gutartig verlaufen ist. Ich habe vor 2 Jahren eine Sippe in der Oberpfalz mit 14 Kranken männlichen Geschlechts untersuchen können, die einen x-chromosomalen Erbgang der Muskeldystrophie zeigt (Abb. 1). Bei den Merkmalsträgern tritt die Muskeldystrophie zwischen dem 12. und 25. Lebensjahr an der Beckengürtel- und Beinmuskulatur auf. Eine Schwäche in den Armen und im Schultergürtel macht sich im allgemeinen 5–10 Jahre später bemerkbar; erst 25–30 Jahre nach dem Beginn des Leidens oder noch später werden die Kranken gehunfähig (Abb. 2–3). Weitere Sippen mit spätem Beginn und gutartigem Verlauf sind die von *Kostakow* und *Derix* [1937] sowie von *Derix* [1938] mitgeteilte Bonner Sippe mit 14 Kranken und einem Verdachtsfall und die Weseler Sippe von *Gummersbach* [1952] mit 15 Kranken männlichen Geschlechts. Bei *Walton* und *Nattrass* gibt es zwei hierhergehörige Sippen (D 9 und D 19) und bei *Levison* [1950] wahrschein-

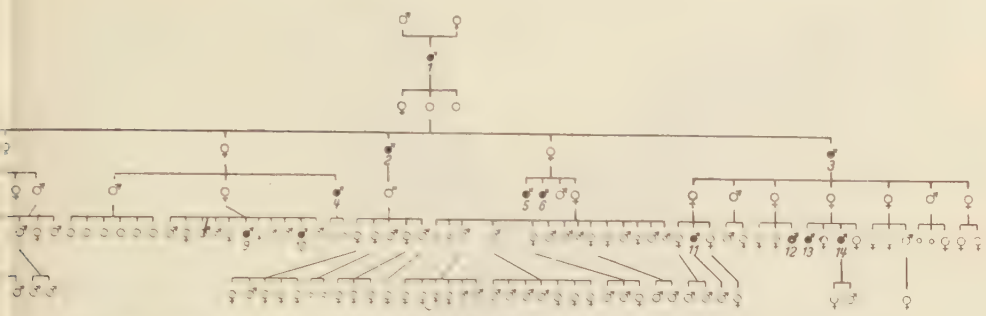


Abb. 1. Oberpfälzer Sippe. ● Kranke mit Muskeldystrophie, ♂ Verdacht auf Muskeldystrophie. ♀♂ Gesunde, ○ Gesunde unbekannten Geschlechts, ♂♀ Im Säuglings- oder frühen Kindesalter Verstorbene, ° Im Säuglings- oder frühen Kindesalter Verstorbene unbekannten Geschlechts, ∞ Zwillinge. (Arch. Psych. Z. Neurol. 193, 1955.)



Abb. 2.

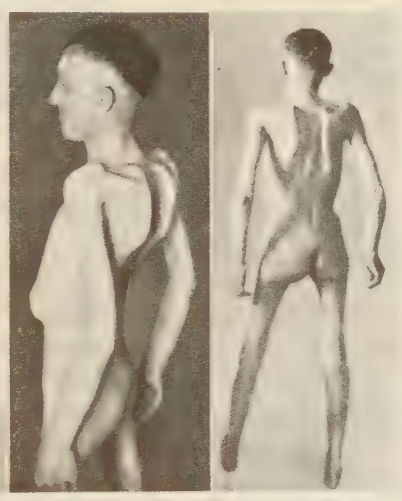


Abb. 3.

Abb. 2. Kranker aus der Oberpfälzer Sippe (H. B., 33 Jahre alt).

Abb. 3. Kranker aus der Oberpfälzer Sippe (B. R., 38 Jahre alt, schwer betroffen).

lich 3 (Fam. 21/21a, 22 und 23). Die Abbildung 4 stellt ein Schema des Altersaufbaus der Kranken der 3 in Deutschland beobachteten Sippen dar. Jeder horizontale Balken entspricht einem Kranken. Die Länge des Balkens bedeutet das Alter, in dem der Kranke aus der Beobachtung ausgeschieden ist, ein Kreuz den Tod. Der Beginn der Schraffierung deutet das Erkrankungsalter an und die schwarze Ausfüllung die Gehun-

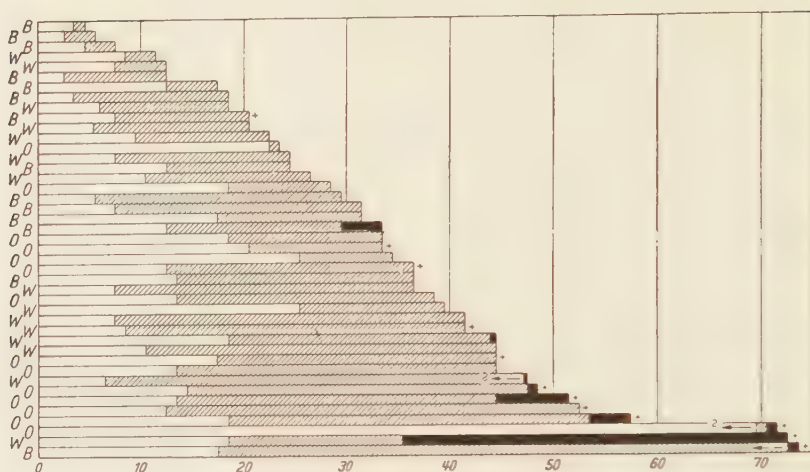


Abb. 4. Neue x-chromosomale Muskeldystrophie. Altersaufbau der Kranken. krank. gehunfähig krank. ← ungenaue Angaben über die Zeit der Erkrankung. (Die Grenze, an der der Pfeil ansetzt, bezeichnet das Alter, in dem die Muskeldystrophie mit Sicherheit vorhanden war.) + verstorben. (Arch. Psych. Neurol. 193, 1955.)

O: Oberpfälzer Sippe, B: Bonner Sippe, W: Weseler Sippe.

fähigkeit. Während das Leiden in der von mir untersuchten Oberpfälzer Sippe im 12. bis 25. Lebensjahr begann, variiert der Zeitpunkt des Beginns in den beiden anderen Sippen stärker. Insgesamt liegt er zwischen dem 2. und 35. Lebensjahr mit einer Hauptgefährdungszeit zwischen dem 6. und 18. Jahr. Aber erst ein Vergleich mit dem Altersaufbau von Kranken des bisher bekannten bösartigen x-chromosomalen Typs (Abb. 5) läßt den Unterschied beider deutlich werden. Bei dieser bisher bekannten x-chromosomalen Muskeldystrophie werden die Kranken regelmäßig spätestens zwischen dem 12. und 15. Lebensjahr gehunfähig. Bei der neuen x-chromosomalen Muskeldystrophie ist das selten vor dem 5. Lebensjahrzehnt der Fall, manchmal noch später, und die durchschnittliche Lebenserwartung ist ganz erheblich günstiger. Abgesehen vom späten Erkrankungsalter und vom gutartigen Verlauf, gibt es im klinischen Bild, soweit bisher bekannt, keine Unterschiede gegenüber dem «Duchenne type of progressive muscular dystrophy of young boys». Erwähnenswert ist noch, daß je 5 Kranke der Oberpfälzer und je 5 Kranke der Weseler Sippe Kinder haben, die erwartungsgemäß gesund sind. In der Geschwisterschaft von Kranken ist die theoretische Krankheitserwartung 25 %; errechnet wurden mit der Methode von Lenz und der Alterskorrektur von Weinberg 25 %, Erfahrung und Erwartung stimmen überein, was auf regelmäßige

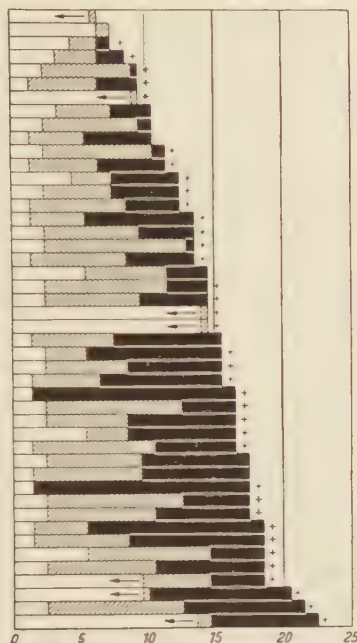





Abb. 5. Nach P. E. Becker: Dystrophia musculorum progressiva. Altersaufbau der Kranken der bisher bekannten x-chromosomalen Muskeldystrophie.  krank,  gehunfähig krank,  ungenaue Angaben über die Zeit der Erkrankung. (Die Grenze, an der der Pfeil ansetzt, bezeichnet das Alter, in dem die Muskeldystrophie mit Sicherheit vorhanden war.)
+ verstorben.

Manifestation der hemizygoten Anlage im männlichen Geschlecht hinweist. Das Allel, das der bisher bekannten x-chromosomalen Muskeldystrophie zugrunde liegt und das der neuen sind wahrscheinlich, da sie beide im X-Chromosom lokalisiert sind, verschiedene Mutationsstufen eines und desselben Gens, dessen gesamte Mutationsrate sich also noch um die des neuen Typs erhöhen würde. Nach grober, überschlagsmäßiger Schätzung dürfte die Mutationsrate der neuen gutartigen Muskeldystrophie ungefähr bei $5 \cdot 10^{-6}$ liegen oder noch niedriger sein.

Außer diesen beiden x-chromosomalen Muskeldystrophien gibt es noch eine rezessive autosomale Muskeldystrophie. Tyler und Wintrobe [1950] und Stephens [1953] kennen sie offenbar nicht. Hanhart [1950] und Pfändler [1950] haben in der Schweiz auf sie aufmerksam gemacht, die Oberibergersippe von Minkowski und Sidler [1928] gehört hierher, in der heute 14 männliche und 11 weibliche Kranke (Hanhart 1954) bekannt sind, die auf gemeinsame Vorfahren zurückgehen. Stephenson hat 23 Familien

untersucht, bei denen er einen rezessiven autosomalen Erbgang angenommen hat. Er nennt diese Form der Muskeldystrophie «limb-girdle muscular dystrophy». In 5 Fällen waren die Eltern blutsverwandt. *Walton* und *Nattrass* haben 18 Familien mit 22 Kranken der «limb-girdle muscular dystrophy» untersucht. Auch sie vermuten, daß der Erbgang in der Regel rezessiv autosomal ist, Blutverwandtschaft der Eltern war einmal nachzuweisen. *Lamy* und *Gronchy* fanden unter 102 Familien mit Muskeldystrophie 9 mit rezessivem autosomalem Erbgang. Ich selbst habe bei meiner Untersuchung in Baden ebenfalls einen rezessiven autosomalen Erbgang feststellen können. Das Erkrankungsalter der Merkmalsträger liegt zwischen dem 2. und 40. Lebensjahr. Das klinische Bild unterscheidet sich, soweit ich es bisher übersehe, in vielen Fällen nicht von dem des gutartigen x-chromosomalen Typs, und einzelne Schwerkranke können dem bösartigen x-chromosomalen Typ gleichen. Bei allen 3 Typen, den beiden rezessiven x-chromosomalen und den rezessiven autosomalen, beginnt der Prozeß am Beckengürtel und den Oberschenkeln: er kann zwar in manchen Fällen sehr bald auch die Schultergürtelmuskulatur ergreifen, aber der zeitliche Vorrang der unteren Extremitäten ist deutlich. Die 3 rezessiven Typen treten klinisch als Beckengürtelform in Erscheinung. Ich fand die Beckengürtelform der Muskeldystrophie in Baden bei 64 Sippen. Wenn man die 26 Sippen herausnimmt, die wahrscheinlich dem bösartigen x-chromosomalen Typ zuzuordnen sind, so verbleiben 38, von denen aber wahrscheinlich noch die eine oder andere zum gutartigen x-chromosomalen Typ zu zählen wäre, was aber bei der klinischen Übereinstimmung beider nicht ohne weiteres zu erkennen ist. In 13 Sippen kommen weibliche Kranke vor, in 5 Fällen sind die Eltern in näherem Grade blutsverwandt, in 7 weiteren Fällen ist auf Grund von Namensgleichheit der Vorfahren beider Eltern, die am gleichen Ort ansässig waren, Blutsverwandtschaft entfernteren Grades zu vermuten. Für die Bedeutung der Blutsverwandtschaft der Eltern beim Homozygotwerden des rezessiven Allels spricht die Verteilung der Familien mit Beckengürtelfällen auf Stadt und Land. Nur $2 \pm 2,1\%$ der Sippen stammt aus größeren Orten mit 10 000 oder mehr Einwohnern, während der Bevölkerungsverteilung nach $23,5 \pm 0,042\%$ aus größeren Orten zu erwarten wären, d. h. die Kranken stammen überdurchschnittlich häufig aus kleinen Orten, aus Dörfern, in denen bis zum 1. Weltkrieg Verwandtenchen meistens entfernten Grades überdurchschnittlich häufig waren. Auf diese Weise konnte das relativ seltene Allel der rezessiven autosomalen Muskeldystrophie homozygot werden. Die Kinderzahl der Kranken bleibt gegenüber der der Durchschnittsbevölkerung erheblich zurück.

Der 4. Typ von Muskeldystrophie ist dominant autosomal erblich. Das klinische Bild entspricht der facio-scapulo-humeralen Form. *Stephenson* kennt ihn nicht; *Lamy* und *Gronchy* fanden ihn unter ihren 102 Familien nicht; *Walton* und *Nattrass* sahen unter ihren 84 Sippen 4 mit insgesamt 22 Fällen, die hierher gehören. *Tyler* und *Stephens* haben eine große Sippe mit 159 Kranken in 6 Generationen beschrieben. Ich selbst habe in Baden 22 Sippen mit Kranken der Schultergürtelform, wie ich sie nennen möchte, festgestellt. Das Leiden beginnt am Schultergürtel (scapulo-humerales Form) oder an der Gesichtsmuskulatur (faciale Form) im allgemeinen zwischen dem 7. und 25. Lebensjahr. Der Verlauf ist meistens langsam und gutartig, die Beckengürtelmuskulatur ist auch in fortgeschrittenem Alter manchmal noch frei oder nur geringgradig betroffen: nur wenige Kranke werden gehunfähig. Der dystrophische Prozeß beschränkt sich auf die Muskulatur, eine Knochen- oder Fettgewebsdystrophie gibt es beim dominanten Typ nicht. Der Erbgang ist annähernd regelmäßig dominant, denn in der Geschwisterschaft von Kranken ergab die korrigierte Auszählung (nach *Weinberg* und nach *Strömberg*) $41 \pm 3.9\%$ und in der Kinderschaft $46 \pm 3.4\%$. Da es in Südbaden, dem Auszählungsbereich, mehrere Sippen mit vielen Kranken gibt, kommt ein Muskeldystrophiekranker des dominanten Typs auf 20 000 der Bevölkerung. Die Mutationsrate haben *Lenz* und ich nach der direkten

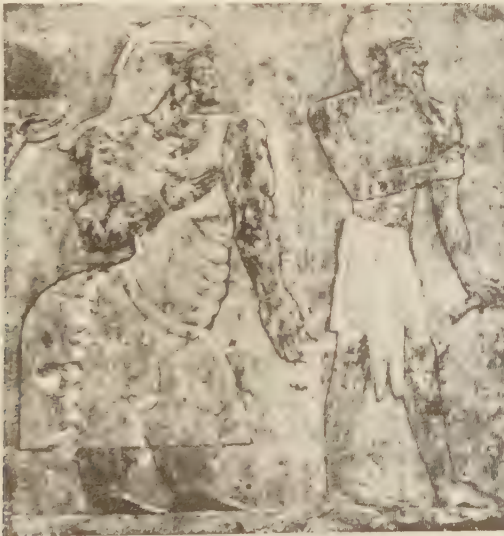


Abb. 6. Aus: Nervenarzt 26, 1955.

Methode auf $4,7 \cdot 10^{-6}$ geschätzt. Diese dominante Muskeldystrophie ist offenbar geographisch nicht gleichmäßig verbreitet, sie ist in den skandinavischen und den angelsächsischen Ländern und in Frankreich vermutlich seltener als in Südwestdeutschland. Zum Schluß zeige ich Ihnen noch das Bild einer Muskeldystrophie, das 3500 Jahre alt ist; offenbar handelt es sich um die dominant erbliche Schultergürtelform. Es stellt die Königin von Punt dar, stammt aus dem Ägypten der 18. Dynastie und wurde am Totentempel der Königin Hatschepsut in Deir El Bahari gefunden (*Pösch* und *Becker* 1955).

De Jong, J. G. Y.: Acta genet. 7, 310-314, 1957

St. Josefsziekenhuis, Heerlen, Holland

DYSTROPHIA MYOTONICA, PARAMYOTONIA AND MYOTONIA CONGENITA

By J. G. Y. DE JONG

In my book of this title which appeared this year [1], I have given the results of a research on 12 families suffering from D.My.

Starting from 11 propositi, I examined 11 families personally. In them were found 45 cases of D.My. and 16 suspicious cases, while in 11 further cases the diagnosis was sufficiently certain from the family case history. Since then, a twelfth family has been found in which 12 new cases of D.My. were encountered and one suspicious case. In all then, we have seen 57 cases of D.My., 17 suspicious cases and 11 that were anamnesticly certain. In all, the genealogies comprise 391 persons of whom 180 were examined personally. Gathering the families in a list and starting from the number of persons examined in one family we get the following picture: The number of sibships is 23, number of live births 167. The number of abortions was given as 1. 29 died in infancy, 15 died later not examined. The number of living persons not examined was 29. Of those examined 34 were not affected by the disease. There were 7 suspicious cases. The number of clear-cut cases of D.My. amounted to 53. In this way we find

the rate to be 34 sound persons as against 53 patients with D.My. and 7 suspicious cases.

It goes without saying that it is not permitted to make use of these figures without taking into account that these families were selected specially with a view to the occurrence of a case of D.My.

Now, if in each of the 23 sibships we subtract one person as *propositus* the ratio becomes 34:(30 + 7). This agrees reasonably well with the rate of 1:1 of a simply dominant hereditary factor. I for one, however, hold that in the future the porportion of patients with D.My. will prove to be considerably higher. For, as it is, the number of these patients is greatly forced down by the fact that in completely examined families with small children there may be e.g. only one patient with nothing but cataract. This child will at the most be counted as a suspicious case, while all the others are noted as not affected. When these persons arrive at middle age, however, a completely different division would be obtained. If we only count the completely examined sibships that have reached middle age we get a ratio of affected to non-affected which is certainly higher than 1:1, especially if all the sufferers from cataract would be counted as suspicious cases. This would bear out the statement made by *Maas* and *Paterson* [2] that in well-examined families the proportion is higher than 1:1. They assume multiple factors and among other things they point out that cataract is one of the symptoms that may breed true. In my book it is described that I saw a certain family with D.My. and that in a second family of the same rather rare name I found myotonic cataract in several family members. The two genealogies did not run together as far back as 1700, although a common ancestor is probable. It is not impossible, though not proved that the cataract had been transmitted for centuries. In this way the number of gene carriers must have become very great. *Maas* and *Paterson* [2] think that the most plausible theory is that there are multiple factors, one for myotonia, one for atrophy, one for cataract, etc. These factors have no, or only a mild effect when isolated, but a very marked effect when united. However, for the time being the assumption of a dominant polyphaenic gene seems the best theoretical explanation.

The proportion of men as against women in our rather limited material was 23 women: 34 men, and among the suspicious cases 8 women:9 men. Among my material there is a family whose members believe that the disease occurs only in the men and is carried only by them, although I did find a slight case of D.My. among the women and also cataract carried by women. Literature has the history of a family described by *Katzenstein* [3], where D.My. was carried on via the male line; a single genealogy by

Thomassen [4] gives a similar impression. Even though in general the data in literature speak in favour of a somatic dominant heredity, yet in future it will be necessary to watch out for a rare sex-linked form.

Time does not permit to go deeply into the theory of progressive heredity, which genetically is so disputable. Up to the present it has always been described only starting from the sequence of cataract—cataract and slight myotonia,—myotonic symptoms, etc. I for one have examined extensively the psychical condition and in many genealogies I found clearly progressive heredity, with much oligophrenia appearing at last.

Fam. A.

Fam. F.

Fam. G. [1]

I saw a large family with paramyotonia, a tendency toward paradoxical myotonia and some pictures that were more Thomsen-like. No cataract was found in several severe cases. There were only slight signs of atrophy, such as ptosis or flat, conically, ending thenar muscles. Here the pedigree comprised 117 persons in all. There were 7 sibships in which the disease was found and of which more than one person was seen. These comprised 49 live births: 8 died in infancy: 19 non-affected and 22 affected. The pedigree (p. Fam. U.) [1] gives a picture of a somatic dominant heredity.

In reviewing the literature, I have not found a single clinching case, proving that ever in a well-examined family D.My. and My. cong. occur together.

In many respects the paramyotonic family seems to be the antipode of Steinert's disease.

The same may hold true for Thomsen's disease, but I have not seen the latter in the last 15 years, although it is striking how closely the features of some of our patients resembled the photographs published by *Thomassen* and others.

Dystrophia Myotonica	Paramyotonia Family U
(1) Alopecia, mainly frontal	Dense thickly implanted hair coming down low frontally.
(2) Hollow-eyed	The eyes are surrounded by a thick wall, protruding forward convexly.
(3) Facies myopathica	Pronounced facial muscles.
(4) Changes of the facial skeleton, e.g. the small distance between the maxillary angles.	Strongly pronounced maxillary angle.
More obtuse angle of the mandibula.	Angle more towards 90°.
(5) Leptosome, asthenic type.	Athletic, sometimes more short pyknic type.
(6) Atrophy of the M. sternocleidomastoid and biceps, triceps, brachioradial.	Sometimes hypertrophy of shoulder-girdle and arm muscles, sternocleidomastoid to a width of 10 cm.

Dystrophia Myotonica

Paramyotonia Family U

- | | |
|--|---|
| (7) After a difficult beginning the forceful movements gradually go more easily. | The forceful movements subsequently get more difficult. |
|--|---|

Somewhat uncertain points:

- | | |
|---|--|
| (8) Psychic picture colored more schizoid. | Psychic picture more cyclically colored. |
| (9) Manifestation from ± 10 years of age. | Congenital. |

Points of difference without antithesis:

- | | |
|--------------------------|------------------------|
| (10) Cataract. | No cataract. |
| (11) Testicular atrophy. | No testicular atrophy. |

I do not want to attribute undue importance to point 7, as also in D. My. we sometimes meet paradoxical myotonia and on the other hand in the other paramyotonic families in literature no paradoxical myotonia has been described.

Concerning point 9, in some cases we may speak of a congenital manifestation of D.My., as e.g. what concerns the shape of the head and in oligophrenia. This is especially true of patients with complete penetration of the gene.

By the side of the points of contra-distinction there exists the conformity of the phenomenon of myotonia. Most of the points mentioned, apart from 6 and 10, seem to hold true also for Thomsen's disease. Vid. e.g. photograph 4 in Thomsen's work.

As a hypothesis that may also have heuristic value, I therefore want to pose the following: There exists an antithetical relation between Thomsen's disease and Steinert's disease; paramyotonia (as in Family U.) occupying a position between the two.

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Discussion

P. E. Becker (Tuttligen): In Familien mit Thomsen'scher Myotonie gibt es vereinzelt Kranke mit leichter, aber deutlicher Atrophie einiger der anfangs hypervoluminösen Muskeln. Vor allem scheinen es die Oberarmmuskeln zu sein, die atrophisch werden, we-

niger die der Unterarme. Derartige Beobachtungen berechtigen nicht dazu, die Thomsen'sche und die Curschmann-Steinert'sche Myotonie als genetische Einheit anzusehen; es handelt sich um zwei verschiedene, selbständige genetische Typen. Wir müssen einsehen, daß das myotonische Verhalten bei der Thomsen'schen Krankheit wohl das obligate, aber nicht das einzige Symptom ist, es kommt ja auch das Hypervoluminöse der Muskulatur hinzu, und wie gesagt, in einzelnen Fällen eine Atrophie ohne Entartungsreaktion.

D. Klein (Geneva): I was very interested to hear that Dr. de Jong in his extensive investigations on myotonic dystrophy in Holland has also come to the conclusion that Steinert's and Thomsen's disease are independent entities. In Switzerland we have now studied about 100 families with 230 living patients affected with myotonic dystrophy and about 10 Thomsen-families and arrived at the same result. As for congenital forms, we had the opportunity to encounter two cases both associated with oligophrenia. In the first, there was, moreover, cranio-facial dysostosis, internal occipital hyperostosis, unilateral radio-cubital synostosis and bilateral pes excavatus, in the second paralytic club-feet. It seems, therefore, that the dystrophic gene in complete polyphenous penetrance has also a tendency to affect the skeletal system.

J. G. Y. de Jong (Heerlen): To *P. E. Becker:* Es ist richtig, daß die leichte Muskelatrophie, die gelegentlich bei Thomsens Krankheit beobachtet wird, nie mit den weiteren Zeichen der D.My. zusammengeht.

To *D. Klein:* There are more cases of club-foot in the literature as for instance those of Fleischer and Lups. But club-foot does not appear in every case with full penetrance.

Kloepfer, H. W. and C. Talley: Acta genet. 7, 314-318, 1957

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AUTOSOMAL RECESSIVE INHERITANCE OF DUCHENNE-TYPE MUSCULAR DYSTROPHY

By H. W. KLOEPFER and C. TALLEY

The occurrence of the Duchenne type of muscular dystrophy in girls has been previously reported, but after a careful review of the literature *Stevenson* [1953] claims that all such cases are atypical and should not be classified as Duchenne type. He states also that if an autosomal recessive gene should cause this type of muscular dystrophy, males and females would be expected to occur in the same sibships, an event not previously reported.

Although agreeing with *Stevenson* that Duchenne type of muscular dystrophy is always associated with a sex-linked gene, *Walton* [1955] includes two girls in his series of 56 cases and states that they "have shown no significant difference in clinical manifestations and course from several of the boys in the series".

The purpose of the present study is to show the existence of an autosomal recessive gene which may best explain the occurrence of Duchenne type of muscular dystrophy in girls. Seven cases of progressive muscular dystrophy (3 males and 4 females, with a boy and a girl in sibship D) occurring in one kindred and one case of a girl in an apparently unrelated family have been studied. The parents of the affected individuals in sibships A, B, C and D of kindred I (Figure 1) are third cousins once removed,

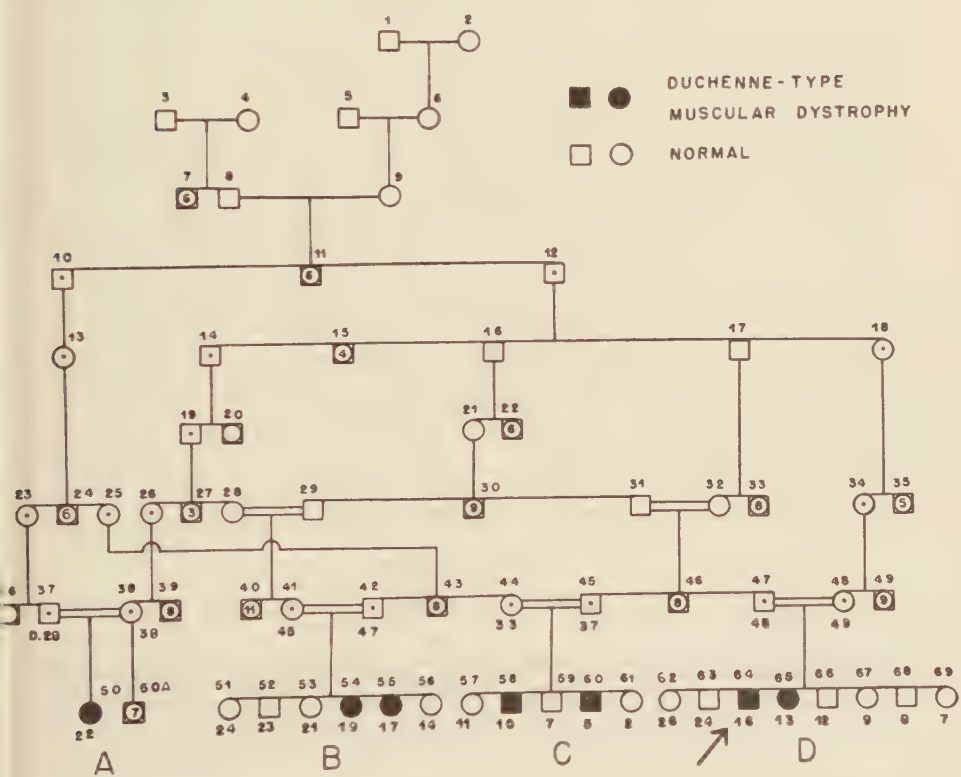


Fig. 1. Pedigree of kindred I showing autosomal recessive inheritance of Duchenne-type muscular dystrophy in a family of Spanish descent. Reference numbers of individuals are above the symbols; numbers within the symbols are the number of individuals, if more than one, represented by a single symbol; and numbers below symbols are ages or ages at death.

third cousins once removed, third cousins, and second cousins, respectively. Individuals I-8 and I-9 were common ancestors to the parents of all affected individuals in this kindred. (Note: The roman reference identifies the pedigree and the arabic numeral the individual.) The parents of II-22 (Figure 2) are second cousins. The gene associated with the muscular dystrophy in these individuals could be 100 % penetrant in the homozygous state.

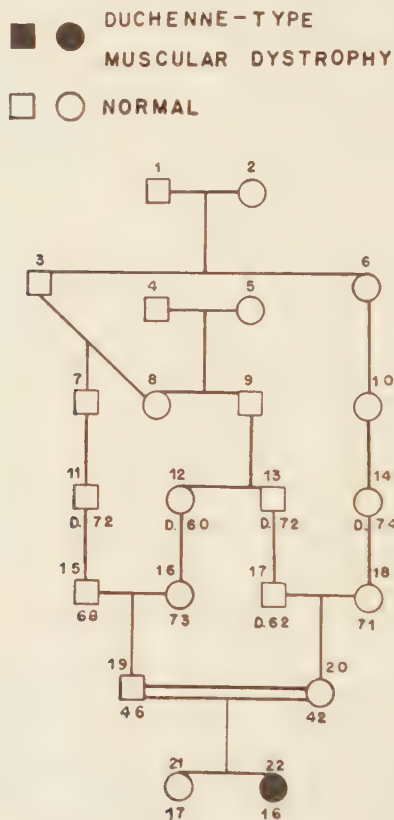


Fig. 2. Pedigree of family II showing autosomal recessive inheritance of Duchenne-type muscular dystrophy in a family of French descent. Reference numbers of individuals are above the symbols; numbers below symbols are ages at death.

A comment frequently entered in the various clinical records of our cases was "typical textbook picture of pseudo-hypertrophic muscular dystrophy except for the fact she was a girl". In all of our cases the clinical descriptions, age of onset, and rate of progress are strikingly similar and

compatible with the Duchenne type of muscular dystrophy, as described by *Walton* and *Natras* [1954]. We agree with the classification as described by these authors except for mode of transmission which we felt should not be limited to a sex-linked recessive gene. We feel that the mode of transmission can be either by a sex-linked recessive gene or by an autosomal recessive gene but the frequency of the former is greater.

In each of our 8 cases the age of onset varied from 5 to 8 years. Weakness in the legs, waddling gait, and pseudohypertrophy of calf muscles were the first signs of onset. At the time of initial examinations, which varied from ages 5-13, there was weakness and wasting of shoulder-girdle and upper arm muscles, lumbar lordosis and scoliosis, and positive Gower's sign. Except for other cases within a sibship, all of the initial examinations were done by different clinicians who were unaware that other cases occurred in the kindred. Inability to walk occurred between ages 16 and 19. In no case was there involvement of facial muscles. Except for the oldest girl in the series who can no longer walk or stand (but who is now pregnant), motion pictures were made of all affected individuals at the ages indicated on the pedigree charts. Six cases have undergone clinical studies, including gastrocnemius muscle biopsies, and creatinine excretion studies, at Charity Hospital of Louisiana in New Orleans. Findings from these studies are compatible with primary myopathy.

There seems to be a need for further studies of the autosomal recessive Duchenne type of muscular dystrophy before this type can be distinguished clinically from the sex-linked recessive type if, indeed, such a distinction is possible. The slightly earlier average age of onset in sex-linked recessive cases and somewhat more rapid rate of progress, as emphasized by *Stevenson* [1953], may turn out to be distinguishing criteria when used with other features, but when used alone these criteria seem insufficient to recognize the genetic type.

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Discussion

A. G. Steinberg (Cleveland, Ohio): I should like to offer some data which support Dr. *Kloepfer's* point. Dr. *Jonathan Cohen* and I have studied a pair of identical twin girls both of whom have pseudohypertrophic muscular dystrophy. The diagnosis was confirmed

by muscular biopsy. We have in addition observed several other cases of pseudohypertrophic muscular dystrophy in girls. Clinically, the course of these patients is essentially identical with that in males. It appears that the autosomal recessive type of pseudohypertrophic muscular dystrophy is more frequent than has previously been considered.

P. E. Becker (Tuttlingen): Das Manifestationsalter liegt bei der rezessiven autosomalen Muskeldystrophie zwischen dem 2. und 40. Lebensjahr. Kranke mit noch späterem Beginn – meistens handelt es sich um Frauen, deren Krankheitsbild als “menopausal muscular dystrophy” bezeichnet worden ist – gehören in der Mehrzahl nicht zu den Muskeldystrophien, sondern zu Polymyositis.

Walton, J. N.: Acta genet. 7, 318–320, 1957

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THE INHERITANCE OF MUSCULAR DYSTROPHY

By J. N. WALTON

The classification of the myopathies or muscular dystrophies has been a source of dispute for many years. In a recent communication, *Walton and Natrass* [1954] reviewed the literature dealing with this subject and proposed a new classification, based upon a study of the clinical features, natural history and mode of inheritance of this group of disorders in a series of 105 personal cases. It was agreed that the rare ocular and distal forms of muscular dystrophy could be recognized as separate clinical entities and that other uncommon and atypical forms of myopathy were seen from time to time. However, it was considered that the commonly-occurring cases of dystrophy fell into three groups which were clinically and genetically distinct. These were entitled the Duchenne, facioscapulohumeral and limb-girdle types. In our experience each of these forms bred true in an individual family. The Duchenne type corresponds to the traditional category of “pseudo-hypertrophic” muscular dystrophy and also to the type which *Tyler and Wintrobe* [1950] have called “childhood dystrophy”. However,

neither of these terms is entirely satisfactory for this group of cases, since pseudohypertrophy is not invariable and may also occur, though less commonly, in the other forms of the disease. The cases of this type without pseudohypertrophy would traditionally have been included in the pelvic girdle atrophic type of Leyden and Moebius, but our experience has revealed that cases of this nature developing in childhood may show a clinical course identical with that which is manifest in others which show striking pseudohypertrophy. Finally, we have also come across a number of families in which this form of the disease, though otherwise typical, did not begin in childhood. For all of these reasons we have preferred the eponymous term "Duchenne" for the identification of this form of muscular dystrophy. The second or facioscapulohumeral type corresponds closely to the traditional category as described by Landouzy and Dejerine. The third type, limb-girdle muscular dystrophy, includes Erb's scapulohumeral form of muscular dystrophy, adult cases of the traditional Leyden-Moebius pelvic girdle atrophic type and the few cases of true muscular dystrophy which first develop in late life. Unlike Stevenson [1953], we are confident that this form of the disease is a separate disorder, both clinically and genetically, from the facioscapulohumeral.

My personal series concerns a total of 208 personal cases of muscular dystrophy. 105 of these were seen in North-East England in 1951-53, the remainder at the National Hospital, Queen Square, London in 1954-55. There were 4 cases of distal myopathy and 9 of ocular myopathy, but the available information was not sufficient to enable me to draw conclusions concerning the inheritance of these rare forms. My subsequent remarks will refer to the remaining 195 cases. Detailed analyses of these cases have been published (Walton [1955, 1956]).

There were 107 cases of the Duchenne type, occurring in 78 sibships of 55 families. 104 were male, and 2 female, while 1 apparent female had nuclei of male type in her polymorphonuclear leucocytes. The latter patient has proved to be a case of Turner's syndrome (ovarian agenesis). The incidence of affected males was estimated as 50 per million and the mutation rate (in the Newcastle cases only) was calculated as 4.3×10^{-5} . All the evidence indicated that this form of the disease, which is usually of early onset and rapid progress, is carried by a sex-linked recessive gene. Our figures also indicate 100 per cent penetrance. The finding of 2 affected females is not incompatible with this suggestion, since it is conceivable that a female carrier could mate with a male upon whose X-chromosome a mutation had occurred. However, the expected ratio of affected females: affected males would be only 1:50,000 unless, as Haldane [1956] has

suggested, the mutation rate is higher in males. Alternatively it is possible that occasional female cases may be due to a dominant mutation. Crossing-over with incomplete red-green colour-blindness was discovered in one family only; there were 5 crossovers in 20 individuals, giving a crossing-over distance of 25 per cent (*Philip, Walton and Smith* [1956]). Although in most families the onset of this form of the disease was, typically, in early childhood, a small number of families were discovered in which the disease, though otherwise typical, began in each affected member as late as the second or third decade. Had it not been for the characteristic sex-linked pattern of inheritance, these cases might, as individuals, have been difficult to distinguish from others of the limb-girdle type.

33 cases of the facioscapulohumeral variety were found, occurring in 20 sibships of 7 families. Of these cases 23 were fully-developed, 10 abortive. These abortive or partially-affected cases are of the greatest importance as the patients may be unaware that they show minimal signs of the disease. Hence for accurate genetic studies, examinations of all available relatives is essential. 8 of the patients were male, 25 female and no isolated cases were discovered. The pattern of inheritance of this form, which may begin at any age and is very benign, is clearly that due to an autosomal dominant gene, though there may be incomplete manifestation or sex-limitation (to females) in some families. In one family, an affected female had affected children by more than one male, confirming that the disorder must almost certainly be due to expression in the heterozygote.

There were 55 cases of the limb-girdle type, occurring in 43 sibships of 41 families. 27 were male, 28 female and 32 of the cases were isolated. Consanguinity occurred in 2 families, while in 1 family 2 affected individuals had an affected parent, an event which, according to our figures, would be expected to occur once in 316 families, if the disorder were due to an autosomal recessive gene. All the evidence from this series of cases favours the latter mechanism of inheritance for this form of the disease, which may begin at any age and is moderately benign.

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HOMOZYGOUS APPEARANCE OF DISTAL MYOPATHY

By L. WELANDER

In a dominantly inherited muscular disease it is most unusual to find offspring of a union of two affected persons. Only *Boeters* [1935] has reported such a family, where both parents had myotonic dystrophy. They had three children, of whom two were affected with myotonic dystrophy of the common type.

A family is reported in which both parents and seven of their 16 living children had distal myopathy. This type of progressive muscular dystrophy was fully described recently (*Welander* [1951]; the pages denoted refer to this work):

The distal late hereditary myopathy is a primary muscular disease and belongs to the group of progressive muscular dystrophies. It is inherited as a dominant trait at least in the great majority of cases (p. 32). Direct inheritance through four generations is found in 6 pedigrees (p. 34), through three generations in 26, and through two generations in 24 pedigrees.

The age at onset observed (in 76 cases, p. 43) ranges from 34 to 82 years; mean 50 years, with a standard deviation of 10 years.

The sex incidence is about 1.5 men to 1 woman. A constant preponderance of men is observed in the affected parents, sibs, and children of both the affected men and women examined (p. 37). A lower disease manifestation in women would seem to be the most probable reason for the sex difference (cf. *Csik* and *Mather* [1938]).

In distal myopathy, as in the other progressive muscular dystrophies, there are no symptoms or signs of involvement of the nervous system nor of the endocrine organs. During life the presence of a primary muscular disease can be confirmed by the characteristic picture on electromyography (p. 56) and muscle biopsy (p. 40), and by the absence of fasciculations also during a prostigmine test (p. 57).

Distal myopathy, in its common heterozygous type, is characterized (p. 45 and 62) by the confinement of the weakness and wasting to the long extensors and the intrinsic small muscles of the distal parts of the limbs. Even when the symptoms have lasted for 25 years or more (32 patients), there is no essential impairment of the distal long flexors, of the proximal limb muscles, or of the trunc or cranial muscles (p. 51).

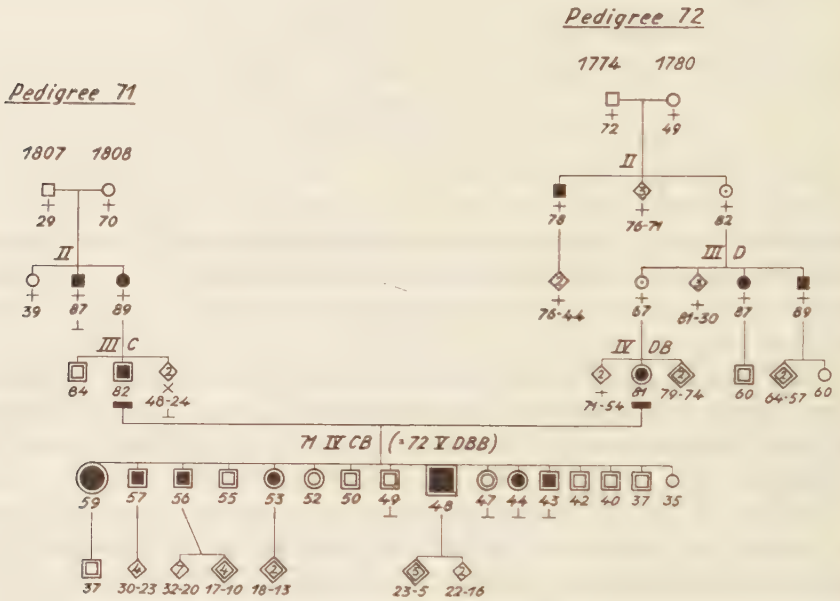


Fig. 1

In the present family (p. 35) both parents (aged 82 and 81) had distal myopathy, of 27 and 19 years' duration respectively. The parents were unrelated, and the same disease was known in the ancestry of both. They had 16 living children, aged 35 to 59; seven had distal myopathy, and nine were so far normal.

If the disease was inherited as a dominant trait, the expectancy of affected children in a family of 16 would be 12, according to the expanded binomial formula. Considering the age distribution (35 to 59 years), and the age at onset observed (range 34 to 82 years, mean 50 years), as a matter of fact this number could not be expected. Which mode of calculation will then give the most faithful expectation?

A simple calculation was performed with consideration only to the age

of onset observed (cf. p. 42–44). If the disease is inherited as a dominant trait, the probability for every child to be a carrier of the trait is 75 per cent. Then, according to their age distribution the expected number of affected children would be 6.34, which tallies rather well with the observed number.

According to *Strömgren* [1935] (cf. also *Schulz* [1936] and *Slater* [1938]), however, the rate of age at onset should be calculated in relation to the age distribution of the population concerned. As regards distal myopathy in this investigation I think the age of onset observed is also very closely related to the age distribution of the 2288 subjects examined. (At that time distal myopathy was not distinguished outside these subjects.) If the calculations are performed both with respect to the age at onset observed, to the age distribution of the subjects examined, and to the total population, the expected number of affected children would be 6.75. Also this agrees rather well with the observed number.

Since one must not forget that there might be a large variation due to chance in such a small clinical material, these figures alone should not be considered as full proof of the dominant inheritance of the trait.

Furthermore, on the assumption of a dominant trait, one third of the affected children would be homozygotes for distal myopathy, and two thirds would be heterozygotes. Is it possible to distinguish between these two genetical types from the clinical appearance of the disease?

In all the seven affected children, the symptoms had begun, as in their parents and in the other typical cases, with weakness and wasting of the distal limb muscles.

In three affected children the course had been typical, with confinement of the disease to the distal long extensors and the intrinsic muscles of the hands and feet after a duration of symptoms for 5 to 17 (mean 9) years.

Two affected children had also some weakness of the flexors of the hips and knees, but were otherwise rather typical after a duration of symptoms for 7 and 9 (mean 8) years (p. 75).

In the two remaining affected children, however, the course of the disease had been grossly atypical (p. 79). After only 4 and 1 years of duration respectively the proximal limb muscles were involved; after 7 and 8 years respectively they were completely incapable of work. At the examination, 14 and 10 (mean 12) years after onset of the disease, they had widespread weakness and wasting of all limb muscles, the trunk and cranial muscles being essentially unimpaired (fig. 5d, p. 62).

The history and observations in these two cases differed considerably from those in the 83 typical cases of distal myopathy with a duration of symptoms for 5 to 14 years, and from those in the 68 typical patients with

a duration of 15 to 44 years (p. 51). It was evident that the two grossly atypical cases had a special type of the disease. And, considering the fact that both parents had distal myopathy, the most probable reason seemed to be that the patients were homozygotes for the gene. The finding of two clinically grossly atypical cases in the sibships of 16 agrees rather well with the expected number, on the assumption of a dominant trait.

If the two grossly atypical cases were homozygous for the gene, then all their children would have inherited the trait. Of their 8 children (p. 35), aged 5 to 37 years, only one had passed the lowest age of onset observed, and he was so far normal. Unfortunately, therefore, this last crucial test for the probable homozygotes must be postponed for some decades.

Summary

The common heterozygous form of distal myopathy is characterized by confinement of the muscular weakness and wasting to the long extensors and intrinsic small muscles of the distal parts of the limbs. The age at onset ranges from 34 to 82 years.

A marriage of two affected persons was observed. It resulted in 16 living children aged 35 to 59 years. Seven children were affected. Two of them exhibited a grossly atypical form of the disease with widespread muscular involvement. There is good reason to regard this grossly atypical form as the homozygous appearance of distal myopathy.

In the calculations of the expected number of affected children the age distribution of the total number of 2,288 examined persons is also considered.

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Discussion

S. Refsum (Oslo) to Dr. Welander: If I remember correctly you said in your monograph, that the weakness occurred first in the hands.

In Norway we have been constantly on the lookout for the distal type of muscular dystrophy since your monograph appeared. We have seen only one patient. He was from Sweden.

Gamstorp, I.: Acta genet. 7, 325-328, 1957

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ADYNAMIA EPISODICA HEREDITARIA

By I. GAMSTORP

The disease called periodic paralysis has been known for at least 70 years. The main symptom is acute, transient paralysis of the muscles of the extremities and of the trunk with free intervals.

Both familial and sporadic cases are on record. In the familial cases the inheritance is said to be dominant with incomplete penetrance, especially among females. The disease usually has its onset in the second decade of life. Free intervals of weeks to months are described as the rule, and the attacks usually last between 6 and 48 hours. During the attack the patient is completely helpless. The respiratory musculature can be involved and cases of death from respiratory paralysis are on record.

Decreased serum potassium is found during the attacks. Attacks can be provoked by the administration of glucose and controlled by the administration of potassium.

My investigation was started in co-operation with Henry Mjönes in January, 1952. A girl, aged 14, was admitted to the Department of Pediatrics, Kristianstad, because of attacks of paralysis, symptoms which the parents had observed since the child was about 1 year old. Familial periodic paralysis was assumed in spite of the fact that the serum potassium examined during 2 attacks was not found to be decreased.

Field studies revealed essentially the same type of symptoms among several of the family members. A number of these were examined at the University Hospital of Lund with the result that an independent disease

could be distinguished. This disease was termed *adynamia episodica hereditaria*.

One hundred and thirty-eight cases could be traced in 2 families, both coming from the north of Scania and called the *Vånga* family and the *Matteröd* family.

The girl I just mentioned was one of the probands of the *Vånga* family. I happened to discover a second proband myself and a third was brought to my notice by Henry *Mjönes*. The fourth proband was a Dane. All 4 probands were traced back to a single married couple born about 1700. I then tried to find as many descendants of this couple as possible and got into touch with all of the hitherto unknown branches. The characteristic could be followed through 5 generations. Only with regard to one woman did the disease possibly skip a generation.

Patients belonging to the family from *Matteröd* were described by *Kulneff* in 1902. Descendants of persons mentioned in his paper were traced. In the *Matteröd* family the disease occurred in 5 generations without a single skipping.

Both sexes are equally affected. Of the children from affected \times unaffected matings in both families and at least 10 years of age—i.e. by when the disease has usually appeared—114 were affected and 116 unaffected while the state of health of 7 was unknown. The disease is transmitted just as often by an affected father as by an affected mother. Sons and daughters of affected fathers get the characteristic equally often. *Adynamia episodica hereditaria* is thus inherited as a monohybrid, autosomal dominant with complete or almost complete penetrance.

In 108 cases the age at onset is known, at least roughly. The disease appears fairly early in life: in about 50 per cent below the age of 5 years, and in more than 90 per cent below 10 years.

Between the attacks the patient is as a rule completely symptomfree. The paralysis begins when the patient is resting, especially soon after physical exertion. The initial symptom is a feeling of heaviness in the extremities. This is followed by increasing loss of strength. After the weakness has reached a maximum, it abates at roughly the same rate as it appeared. The spread and severity of the paresis varies from slight weakness of a single extremity to widespread paralysis in which the patient cannot turn over or get up without help. As a rule, however, loss of strength is not complete. The respiratory muscles are seldom involved, and if so, only slightly. As far as I know, no attack has ever been fatal. The musculature innervated by the cranial nerves is occasionally involved in about half of the patients.

The frequency of the attacks varies from several per day to one or two per year. About three fourths of the patients had an attack on the average at least once a week. The attacks last from a few minutes to a few days. In three fourths of the patients the attacks never lasted more than one hour.

By gentle exercise the patient can ward off or shorten an attack. Hunger favours the occurrence of attacks. Eating, especially bread, has a good prophylactic and therapeutic effect. The patient is thus able to walk off or eat off an attack.

I had the opportunity of examining 51 patients in their homes. Routine clinical examination during a free interval revealed nothing of interest. In addition, 17 patients (11 males and 6 females) aged 4 to 60 years were admitted to the University Hospital of Lund for a thorough investigation between and during attacks. There attempts were also made to provoke, prevent and control attacks.

The attacks were precipitated by rest after physical exertion such as a long walk, cycling or football. Since it was found that the symptoms could be elicited by the administration of 2 to 4 g of potassium chloride by mouth, this method was used alternately with the former, i.e. rest after exertion.

The patients were studied during altogether 61 attacks. The attacks consisted of flaccid paralysis usually beginning in the legs and spreading rapidly to the arms and trunk. In half of the attacks the tendon reflexes were weakened or absent. A common initial symptom was paresthesia of the face, hands and feet. No other disorders of sensitivity were noted. Consciousness was always preserved.

The serum potassium was determined before exertion or before the administration of potassium, after exertion and then every half hour until the paralysis had appeared and disappeared. The determinations were made by flamephotometry. In 45 out of 49 attacks the serum potassium increased to reach a maximum which coincided within ± 15 minutes of the clinical culmination, and then, on abatement of the paralysis, it returned to its original level or somewhat lower. The increase lay between 0.2 and 2.6 mEq/l. The highest level recorded was 7.4 mEq/l in an attack not precipitated by the administration of potassium.

The excretion of potassium in the urine did not decrease before or during an attack but tended to increase.

Electrocardiograms were taken at the same time as the potassium determinations were made. The increase in the serum potassium was accompanied by higher and more pointed T-waves and slight tachycardia.

In 10 out of 11 cases intravenous injection of calcium during an attack rapidly controlled the symptoms.

Glucose administered before or in combination with an otherwise provocative dose of potassium had a good prophylactic effect in 5 cases studied.

Four patients were examined electromyographically by Professor *Buchthal* of the Neurophysiologic Institute, Copenhagen. During the attack the innervation pattern changed suggesting loss of active muscle fibres, and the mean action potential duration was significantly lower than before the attack.

The diagnosis of adynamia episodica hereditaria can often be established on anamnestic grounds. Objective verification requires that an attack be precipitated either by rest after physical exertion or by potassium per os. A dose of 2 g of potassium chloride can be used for small children, 3 g for older children and 4 or possible 5 g for adults. These doses will practically always elicit symptoms in patients with adynamia episodica hereditaria but never in normal individuals. Potassium should, however, not be given to persons with heart disease or impaired renal or adrenocortical function because in such persons even a small dose may have a toxic effect. No matter which way an attack is provoked, the serum potassium and/or the electrocardiogram should be studied on at least 3 occasions: before the attack, at culmination and after the attack. A transient increase in the serum potassium or electrocardiographic changes typical of hyperpotassemia gives the diagnosis.

As yet no treatment of the disease *per se* is available.

A preliminary report of this investigation was given by *Gamstorp, I.* and *Mjönes, H.*: Familial periodic paralysis—a syndrome or a clinical entity? *Folia Hered. Path.* 5, 87, 1956.

The entire material was published by *Gamstorp, I.*: Adynamia episodica hereditaria. *Acta paediat.*, suppl. 108, 1956.

Discussion

W. Hirsch (Tel-Aviv): I want to ask the speaker, if in the extraordinarily interesting cases she has seen other signs of hyperpotassemia, as nausea, oliguria progressing to anuria, intestinal colic, diarrhea. As I have never seen such attacks in hyperpotassemia, it seems that in adynamia episodica hereditaria, hyperpotassemia is only a symptom but not the real cause of the disease.

I. Gamstorp (Lund): Before and during the attacks, the excretion of water and potassium was not decreased. At the culmination of about one third of the attacks I observed cold sweat, general unrest and nausea but no vomiting nor diarrhea. You must remember that the serum potassium was increased for only about 2 hours or—as a rule—less. There was not time enough for other symptoms of hyperpotassemia to occur.

Deventer, Holland

HEREDITARY DIPLEGIA SPASTICA

By J. W. BRUINS and C. H. SIMONS

The researches here described were made in an area surrounding the village of Terwolde and particularly in a stretch of country between this little place and Apeldoorn and known as Broelandervijk, in the middle east of Holland. The families which supplied the material for this study—cases of “neuropathic heredity” (*Hyman*), all belonged to the group of small but prosperous farmers and all, without a single exception, belong to the same religious community (Roman Catholic). So the material is all derived from the same social stratum and the representatives have the same creed: two factors which tend to limit the choice of a life-partner.

Of the 179 members of these families which we examined, 15 (0.009) showed the syndrome of hereditary *diplegia spastica*, as described by *Strümpell*. The first to call attention to the family character of this complaint was *Jendressch*. The percentage as called above seems to us high as compared with that stated in the literature of the subject. *Williams*, for instance, describes a family of 250 persons in which 6 cases of spastic paralysis occur, some of them including cerebral symptoms. In any case our percentage is higher than that found among the average population, for it is a rare complaint. There are no statistics either for the Netherlands or for other countries, at least none dealing with “pure” *Strümpell*. *Adler* states that in the State of Israel “cerebral Palsy” (*Little*), which some research workers regard as a phaenotypical variant of the same genotype, occurs in 750 of the 1,400,000 inhabitants (0.005). This comparison is not entirely correct, but it gives us an idea. In the family circle under consideration the disease occurs at least 18 times as often as it does among the average population of Israel. The accumulation in the family is very evident, while there are no demonstrable exogenous moments that play a causal part in the genesis; no noxas, to be specific, that have excited an unfavourable

influence on the prenatal morphogenesis. Notably, there was no sign of preceding attacks of fever, such as *Adler* mentions.

Clinical symptoms

The neurological symptoms of the hereditary disease may be classed as the pure form of diplegia spastica as described by *Strümpell* in his time. It is a serious disorder of the pyramidal tract, which can manifest early in life—in our material the time of the onset varied between 18 months and 30 years and then proceeds slowly on its unfavourable course. The macroforms are characterized by a spastic-paretic gait, decreased muscular strength in the legs and a slight atrophy of the muscles of the lower leg with symptoms of loss of function of the pyramidal tract. Sensibility, both superficial and deep, is normal. The functioning of the urinary bladder is also intact. The head, arms and thorax are unaffected. The aberrations of the pyramidal tract may be localized by reason of their symptomatology in the thoracal, in the present case the lumbar segment of the medulla.

The pedigree also shows that this disease chiefly affects males: 11 men as against 3 women showed all the symptoms completely. This agrees with the reports of many investigators. Of the 121 children of the fourth generation 6 show the full predisposition, while 8 have micro-symptoms, such as a too lively Achilles tendon reflex and in some cases a positive Babinski. *Klingler* found among 140 members of the family 4 manifest cases and 6 formes frustes. Whether the formes frustes are symptoms of a partial disposition complete in itself due to multiple allely or micro-symptoms of the full predisposition with only little expression is a question which cannot be answered off hand. They are either homozygots only very partially come to expression or heterozygots with so called “stigmata degeneraciones”, at least when the hereditary transmission is recessive. It is certain that our material is not coloured by these stigmata degeneraciones, by accidental symptoms that reveal a wrong disposition. *Jackson* c. s. states, for instance, that among near relatives there has been an extraordinary number of chronic inebrates, mental defectives, mental degenerates, epileptic persons and criminals. In *Bremers* exceedingly interesting report of a family comprising six generations of affected people, he noted and stressed a gradual degeneration in the social status of the succeeding generations. In *Williams* series are found generation after generation of people in the lowest social order. *Thums* also notes this (prognaty and microdentia) as does also *Klingler* (changes of the skin).

Nothing of all this was found in the present study. The representatives of the large family under consideration almost all belonged to the class of

well-to-do farmers, with a normal and in some cases supra-normal mental standing. The process of degeneration was limited to the spinal cord, without affecting the cerebrum or cerebellum. As regards the age at which the symptoms begin to show themselves: it should be noted that this cannot always be determined exactly. This lingering disease begins insidiously, as it were, with slight symptoms which are not always noticed immediately. The data furnished us by the family regarding the onset varied from 18 months to 30 years of age, with an average of 11.6 years. There was certainly a noticeable difference between the third and fourth generation. In the third generation the trouble begins between the ages of twenty and thirty; in the fourth much earlier, namely between eighteen months and two years. The material is too scanty, however, to furnish significant statistics. *Strümpell* records the onset as between the ages of 20 and 30. *Bremer* says that in 59 % of the cases the onset occurs before the eighteenth year.

Method of transmission by heredity

It is advisable to endeavour to discover the action of Mendelian laws when studying heredity in man. The simpler and more sharply defined (radical character) the trouble to be diagnosed, the easier the above is. Especially, too, if the disease is rare and confined to a certain milieu. The monogenetical transmission becomes more evident as the material gains in homogeneity.

In our material this condition is more or less satisfactory: in every case it concerns a pure degeneration of the pyramidal tract with no admixture of extra-pyramidal symptoms or stigmata degenerations, which are certainly connected somehow with the original symptom.

In the literature on the subject we find that the authorities by no means agree as yet as to the process of transmission. *Bremer* collected from the books 100 pedigrees and in 15 cases he found a dominant heredity, particularly in the series showing pure diplegia spastica. 60 % were recessive, 25 % were uncertain. *Klinger* c.s. found one dominant with varying expression and penetration. *Bogaert*, who discovered 4 cases with, in addition, extra-pyramidal symptoms, found dominance in 3 of them and in 1 recession. *Biernond*, too, published a pedigree which showed dominance, although it was too small to justify definite conclusions. None, however, of the hereditary cases he gives belong to the pure type of diplegia spastica, but reveal also extra-pyramidal symptoms.

This research, as well as the researches of *Peron* with his collaborators, *Bickerstaff*, *Garland*, *Freund*, *Philipp*, *Appel* c.s., *Schwarz*, *Heuyer* c.s. and *Michaux* c.s. points clearly to the hereditary character of these disorders.

At first glance it is not a simple matter to discover the method of transmission from studying the pedigree. It would seem as if the fact that the disease occurs in four successive generations clearly shows dominance—dominance, that is to say with varying penetration and expression. Only the representatives of the 4th and 5th generation could be subjected to personal examination, while for the 1st and 2nd only catanamnestic information was available. On the other hand, the case for dominance is greatly weakened by the fact that only six out of the twenty-six children, one of whose parents was affected with the disease to its full extent, show all the symptoms. Surely, even in the case of heterozygotic dominance about 50% may be expected. Suppose we count the two children in the 4 families that show microsymptoms, even then we do not reach 30%. In spite of the fact that the same applies in the case of combined homozygotic and heterozygotic recessive genes we feel we must see in the present case *recessive* transmission. Simple autosomal recessive. The most telling objection to dominance is furnished by families No. 13 and 14. If we may attach importance to the clear and perfectly satisfying catanamnestic data, in both families the father suffered from spastic paralysis. None of the eleven children, nor any grandchild showed a single symptom suggesting diplegia. It is quite certain that these men married women who in the locus concerned of the chromosome had not the gene that carried the character. As a matter of fact no neurological disorders had occurred in the families to which these women belonged. Hence in the cases where the children were affected with the syndrome in question we are dealing with the combination $rr \times Rr$. In case No. 2, where the parents show no external symptoms of the disease, one of the children suffered from diplegia. This argues recession. The mother who had had 2 brothers and 1 sister with diplegia, was undoubtedly heterozygotic and married to a man who was probably heterozygotic also, considering that he was a brother of the grandfather of the 3 diseased children belonging to the family No. 3. Further, in the cases No. 3 and 4 there was a family relationship between the husband and wife. In the first case they were cousins of the 4th grade, in the second of the 3th grade. In cases 2, 9, 13 and 14 where the 21 living children, except two with microsymptoms (stigmata of heterozygotism?) there cannot possibly be any family relationship between the parents, the man and woman with spastic paralysis are both married to partners who are normal themselves and belong to families in which the disease does not occur.

The numerous children in all the families have made fairly plain the method of transmission. In the first generation 3 children were normal and 3 diseased. The great-grandmother suffering from spastic paralysis (No. 1)

was obviously married to a man in whose germ-cells the recessive character was present in single potency, in spite of the fact that we have not been able to show the family relationship higher up.

Summary

A description is given of the results of a study made of members of a family where in four successive generations hereditary diplegia spastica occurred. 15 of the 179 members show the complete syndrome as described by *Strümpell* in his day. A clinical description is given. The hereditary transmission which may present the appearance of dominance, is in reality simply autosomatic recessive.

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ELEKTROENCEPHALOGRAPHISCHE UNTERSUCHUNGEN AN GESUNDEN ZWILLINGEN

Von F. VOGEL

Lenz sagte einmal: «Tatsächlich... findet man bei jeder physiologischen Eigenschaft einen größeren Unterschied von ZZ als von EZ... Zwillingsuntersuchungen über physiologische Eigenschaften werden daher... nichts grundsätzlich Neues ergeben... Trotzdem haben sie auch in Zukunft einen gewissen praktischen Wert. Sie werden... den Kliniker allmählich an den Gedanken gewöhnen, daß die Grundlage aller Reaktionsmöglichkeiten des Organismus in der Erbmasse liegt.»

Ich teile die aus diesen Worten sprechende Skepsis durchaus. Trotzdem hätte ich meine EEG-Untersuchungen nicht unternommen, wenn ich mir davon nur einen psychologischen Effekt auf die Kliniker versprochen hätte. Sondern eine Zwillingsanalyse physiologischer Merkmale darf sich eben nicht damit begnügen zu konstatieren, daß EZ ähnlicher sind als ZZ. Es ist zu berücksichtigen, daß man ja nur eine winzige Stichprobe aus einem lebenslangen Kontinuum erfaßt und daß man praktisch niemals fehlerfrei messen kann. Die wichtigste Frage, die es zu klären gilt, lautet deshalb: Sind die gefundenen Unterschiede zwischen EZ konstant und reproduzierbar, oder entsprechen sie nur dem Stichprobencharakter der Untersuchung, also der physiologischen Schwankungsbreite und dem Meßfehler? Und wenn sie konstant sind, was ist ihre Ursache?

Nicht zuletzt darin, daß man hierauf nicht achtete, ist es begründet, daß die bisherigen Zwillingsuntersuchungen am EEG des Gesunden (*Davis; Raney; Lennox, Gibbs und Gibbs*) zwar einen allgemeinen Hinweis auf die Beteiligung der Erbanlage, jedoch keinen genauen Aufschluß über die umweltbedingte Variabilität des ererbten Musters ergaben.

Ich selbst untersuchte 208 durch die öffentlichen Schulen und Hochschulen Berlins gewonnene gleichgeschlechtige Zwillingspaare im Alter zwischen 6 und 30 Jahren mit Schwergewicht bei den 10–15jährigen. Darunter waren 110 EZ und 98 ZZ. Das EEG wurde mit einem 16kanäligen Gerät abgeleitet; wir untersuchten die beiden Paarlinge gleichzeitig mit je 8 Ableitungen. Das ist wichtig, weil das EEG einem Wechsel der äußeren Bedingungen gegenüber sehr empfindlich ist. Außer in Ruhe wurde bei Hyperventilation und Sauerstoffmangel abgeleitet. Daneben wurde bei fast allen Personen auch das Eintreten des natürlichen Schlafes kontinuierlich am Gerät verfolgt.

Beim Auswerten der Kurven bemühten wir uns zunächst, möglichst viel zu messen und mit statistischen Methoden zu vergleichen; denn «allgemeinen Eindrücken soll man nie trauen» (*F. Galton*)! Wir maßen am Ruhe-EEG folgende Merkmale:

1. Der Grundrhythmus, am deutlichsten sichtbar bei den occipitalen α -Wellen, ist bei den EZ gleich, bei ZZ in etwa zwei Drittel der Fälle verschieden.

2. Beim α -Index (Percent time α) deuteten wir, wie bei den folgenden Maßen, die Differenz zwischen linker und rechter Seite bei einer Person als Maß für den Stichprobencharakter der Untersuchung. Die Unterschiede zwischen EZ waren nicht größer als die zwischen den Seiten einer Person, während ZZ wesentlich verschiedener waren.

3. Ein neu eingeführtes Maß sind die Subalpha-%. Sie werden bestimmt, indem man zunächst mittels eines neu eingeführten einfachen Planimeters beiderseits auf einem 60 cm langen Kurvenstück alle Wellenlängen mißt und dann den Anteil der Wellen unter 133,3 sec. errechnet. Auch hier war präzentral wie occipital der Unterschied zwischen EZ nicht gesichert größer als der zwischen den Seiten einer Person.

4. Ebenfalls mit oben genanntem Planimeter wurde die durchschnittliche Amplitude bestimmt. Die Differenz bei EZ lag nur wenig über der bei einer Person, die bei ZZ ganz wesentlich darüber. Bei der Kontinuität der α -Wellen, einem von *Motokawa* angegebenen Maß für ihre Regelmäßigkeit, ließ sich kein Unterschied zwischen EZ finden.

5. Ein weiteres wichtiges Merkmal ist die Phasenkoordination, d. h. der Prozentsatz der occipitalen α -Wellen, die rechts und links in der Phase übereinstimmen. Die Messung mittels unseres Planimeters ergab keinen größeren Unterschied bei EZ als bei aufeinanderfolgenden Messungen an einer Person, während die Differenz bei ZZ um ein Mehrfaches größer war.

Außerdem wurde eine ganze Reihe qualitativer Merkmale bestimmt; nirgends fanden sich Unterschiede bei EZ.

Der intuitive Eindruck von der individuellen Besonderheit jeder Kurve und der Gleichheit bei EZ geht jedoch über das Meßbare hinaus. Zum Beweis dieser nur intuitiv erfaßbaren Gleichheit machten wir den von *Travis* und *Gottlob* für Ableitungen bei den gleichen Personen angegebenen Identifizierungsversuch: Aus jeder EZ-Kurve wurde ein 30 cm langes Stück herausgeschnitten. Dann breitete eine Hilfskraft alle Stücke der Paarlinge II auf Tischen aus, und ich versuchte, die Abschnitte von Paarling I nun dem richtigen Partner zuzuteilen. Gelang der Versuch, so wurden beide Kurvenstücke fortgelegt. Auf diese Weise war es mir sofort möglich, von 114 Paaren (dabei 4 Kontrollen; vgl. unten) 95 (83,3 %) richtig zu identifizieren. Mit den restlichen 19 wurde der Versuch wiederholt; er gelang jetzt bei 14. Die übrigen waren nicht etwa verschiedener, sondern es können eben auch einmal 2 fremde Paare sehr ähnlich aussehen.

Bei den Belastungsversuchen stellten wir ebenfalls keine konstanten Unterschiede zwischen EZ fest.

Besondere methodische Probleme bot das Schlaf-EEG, da man hier nicht sinnvoll messen kann. So war es nötig, einen möglichst genauen Merkmalsvergleich – ähnlich dem bei der Eiigkeitsbestimmung verwandten – auszuarbeiten. Während die interindividuelle Variabilität besonders in den ersten Einschlafstadien sehr groß ist, fanden sich praktisch keine Unterschiede zwischen EZ. Bei drei Paaren zeigte sich eine kleine Differenz im zweiten Stadium bei Ausbildung der «humps». Als wir den Versuch etwa 1 Jahr später an zwei von ihnen wiederholten, hatte sich die Differenz bei einem erhalten, während man sie bei dem anderen nicht nachweisen konnte.

Gegen das Verfahren, die Seitendifferenzen bei einer Person als Ausdruck des Stichprobencharakters der Untersuchung anzusehen, kann man einwenden, sie könnten ja auch reell und durch die funktionelle Seitendifferenzierung des Gehirns bedingt sein. Um diesen Einwand zu prüfen, wiederholten wir bei 15 EZ alle Untersuchungen etwa 1 Jahr später. Es zeigte sich, daß die Seitendifferenzen und die Differenzen bei EZ weder konstant reproduzierbar sind, noch in irgendeiner Beziehung zur Händigkeit stehen. Damit ist erwiesen, daß sie tatsächlich nicht reell sind. Eine Ausnahme macht hier die Amplitude: es spricht jedoch alles dafür, daß die kleine Differenz sekundär durch etwas verschiedene Beschaffenheit der leitenden Medien verursacht ist; denn eine Beziehung zur Händigkeit ließ sich auch hier nicht nachweisen.

Ferner wurde die Ansicht von *Raney* widerlegt, daß EZ sich im EEG spiegelbildlich verhielten und daß die Seitendifferenzen bei einer Person bei EZ-Paarlingen größer sei als bei anderen Personen.

Ein einziges EZ-Paar, 12jährige Jungen, macht eine Ausnahme: Ein deutlicher, fast über 2 Jahre hin konstanter Unterschied besteht darin, daß bei Paarling II die α -Wellen occipital weitgehend durch träge α -Äquivalente ersetzt sind. Derartige α -Äquivalente sieht man sonst durchaus auch konkordant bei EZ. Ursachen für das diskordante Verhalten dieses Paares ließen sich trotz aller Mühe nicht finden.

Wir schließen aus unseren Untersuchungen, daß die Variabilität des EEG in Ruhe, im Schlaf und bei Belastung unter normalen Bedingungen bis auf seltene Ausnahmen ausschließlich durch die Erbanlage bedingt ist. Da das EEG sich mit der Gehirnentwicklung etwa bis zum 20. Lebensjahr beim einzelnen Menschen sehr erheblich ändert und diese Änderung einem individuell sehr verschiedenen Rhythmus folgt, ergibt sich angesichts der Altersgliederung des Materials, das wir untersuchten, daß auch dieser Rhythmus streng erblich ist. Das wird besonders anschaulich, wenn man die gemeinsame Reifung bei EZ über längere Zeit hin verfolgt. Dagegen können ZZ, obwohl sie ja auch gleich alt sind, einen sehr verschiedenen Reifungsgrad aufweisen.

Ich möchte glauben, daß dieses Resultat im Gegensatz zu der oben zitierten pessimistischen Auffassung auch eine gewisse theoretische Bedeutung hat.

Die vorliegenden Untersuchungen wurden durch die Deutsche Forschungsgemeinschaft und den Stifterverband der deutschen Wissenschaft ermöglicht.

Discussion

F. Vogel (Berlin): Bei allen eineiigen Zwillingspaaren mit Ausnahme des oben genannten Paares, auch bei denen, die im Identifizierungsversuch nicht auf Anrieb klassifiziert werden konnten, war das EEG praktisch gleich. Zur Anbringung der Elektroden verwandten wir – entsprechend dem bei uns üblichen Routineverfahren – Gummibandhauben, die zum Durchstecken der Elektroden Löcher enthielten. Dieses Verfahren gestattet es, relativ genaue Ableitpunkte festzulegen.

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APPLICATIONS OF EPIDEMIOLOGICAL METHODS TO THE STUDY OF CONGENITAL MALFORMATIONS IN MAN

By A. C. STEVENSON

This paper points to the many disconnected contributions to knowledge from animal experiment embryology and human morbid anatomy which tend to be ignored in planning epidemiological investigations in man.

Will be published complete in *Ulster Medical Journal*.

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CAPILLARY ANGIOMATOSIS OF THE CENTRAL NERVOUS SYSTEM

By A. LINDAU

Angioblastomas of the brain form about 2 per cent of all intracranial tumours. Their site of predilection is the hindbrain, especially the cerebellum, comprising almost 10 per cent of the total number of posterior fossa tumours. These cerebellar angiomas have a marked tendency to produce cysts with increasing pressure in the adjacent brain substance. It is generally agreed among neurosurgeons that of all intracranial tumours these

cerebellar angiomas are about the most favourable for operation. This is one reason why they have attracted a good deal of interest, in spite of their rareness. Accordingly, it is important to be able to diagnose them clinically. In most cases they give only diffuse symptoms of increased intracranial pressure without focal signs; this often makes it necessary to resort to ventriculography and vertebral angiography. Vertebral angiography reveals in a quite remarkable way these highly vascular growths, and thereby shows not only the localization but also the size of the tumour before operation. (See figures 57 and 58. *Radner*, *Acta radiologica*, suppl. 87, 1951.) More than 80 per cent of the cases are now saved by operation.

There are, however, some drawbacks. The hereditary and familial incidence of this special kind of tumour has been stressed by many authors, and will be dwelt on by Dr. *Larson* in the next paper. Further in about 10 per cent of the cases the angiomas are multiple; a fact that makes it necessary to be somewhat careful about the final prognosis. In the same way as acoustic neurinomas are mostly solitary but may in certain cases form a part of a generalized neurofibromatosis (*Morbus Recklinghausen*), angiomas of the hindbrain most often occur as single tumours but now and then they may constitute part of a systemic disorder. This syndrome was described 30 years ago (1926) and given the name angiomatosis of the central nervous system. In view of its accepted heredity we thought the disease might be of some interest to a genetic audience.

This table gives the main features of the systemic disorder in question.

Angiomatosis of the central nervous system

Angioblastomas of	cerebellum	}	sometimes
	medulla oblongata		multiple
	spinal cord		(about 10 per cent)

Angiomatosis retinae (von Hippel's disease) bilateral in about 35 per cent.
(About 1/5 of these cases develop brain lesions.)

Visceral lesions

Scattered cysts and hypernephroid tumours of the *kidney*.
(occasionally palpable)
Cystic *pancreas* (or microscopical cysts)
(In adults almost pathognomonic of the syndrome).
(*Epididymis*: Tubular adenomata. Palpable.)
As the lesions of the abdominal organs never cause symptoms during

life it seems appropriate to name the syndrome angiomatosis of the central nervous system.

These multiple tumours and malformations, occasionally showing a family incidence, are apparently of a dysontogenetic origin which ranks this complex together with some other systemic disorders of the brain as tuberous sclerosis, generalized neurofibromatosis and Sturge-Weber's disease. Sturge-Weber's disease is also characterized by angiomatous brain lesions but of quite another type, and hereditary occurrence is doubtful. As these two types of angiomatosis never occur in one and the same individual—possibly with the exception of one case described by *van Bogaert*—or in the same family, it seems that there are good reasons to keep the two types apart.

Angiomatosis of the central nervous system and its coordinated visceral lesions must be considered as resulting from a faulty integration of the components of the diseased organs in regions where the embryonic development is known to be specially complicated. Judging by the foetal termination periods in the different organs one might assume a disturbance occurring in the third month or perhaps even earlier. This leads to cyst formation and the detachment of microscopical clusters of cells capable of giving rise to true tumours (hamartoblastomas) in later life. Such "tumour seeds" have been observed microscopically in an otherwise normal retina in cases of angiomatosis. (See Figure 6, *Lindau*, Proc. roy. Soc. Med. Vol. 24, 1931.)

The cerebellar angiomas generally begin to give clinical symptoms about middle age and about a decade earlier in women than in males as seen from this diagram representing 70 cases from *Olivecrona's* clinic. (See Fig. 2, *Olivecrona*, J. Neurosurg. Vol. 9, 1952.) The reason why they begin to grow at this age is not known. Recurrences following operation have been reported but seem to be due to tumour tissue left at operation or to the existence of multiple angiomas. Metastasis are never met with.

Since 1928 when *Cushing* and *Bailey* published their surgical experiences with angioblastomas the therapeutic results have improved very much and many patients have been saved. But these patients may ask a rather baffling question: what are the chances of my children having the same kind of disease? It is only by careful long term genetic studies that this question can be answered. This topic is discussed by Dr. *Larson* in the next paper.

A quite recent survey of angioblastomas with a comprehensive list of literature is given by K. Y. *Zülch* in *Handbuch der Neurochirurgie (Olivecrona, Tönnis)*. Vol. 3, pp. 455-467.

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CAPILLARY ANGIOMATOSIS OF THE CENTRAL NERVOUS SYSTEM (LINDAU'S DISEASE) GENETIC ASPECTS

By C. A. LARSON

This report is concerned with the incidence of clinically manifest angioblastomas in Sweden. The bearings of the calculated incidence rate on the genetic analysis of capillary angiomatosis is briefly discussed.

According to official statistics the annual tumor mortality in Sweden was, in 1950, $11,000:7,000,000 = 1.6:1,000$. Of 110,081 diagnosed tumors on record in the Danish Cancer Register (by courtesy of Dr. J. Clemmesen), 2,104 were brain tumors. Angioblastomas amounted to 1.6 per cent of surgically treated intracranial tumors in a Danish series (Broager [1949]) of 2,065, and to 2.4 per cent in a Swedish series of 5,250 (Olivecrona [1955]). If no angioblastoma patients were saved by surgical intervention, $0.02 \cdot 0.02 \cdot 11,000 = 4$ annual deaths would be caused by angioblastomas.

The premises of this conjecture are loaded with several inconsistencies. Close agreement cannot be surmised between incidence rates of angioblastomas in operation series and the mortality from angioblastomas in the general population. Brain tumors may constitute a different proportion of all diagnosed tumors as compared with tumors recognized as causing death. Further, surgical treatment definitely affects the death rate from angioblastomas.

The latter source of uncertainty could be eliminated by using death-rates from the pre-surgical era of the angioblastomas. In 1915 7,000 tumor deaths were on record in a population of 5,700,000, i.e. $1.2:1,000$. Had recent diagnostic attainments permitted a more complete recognition of tumors as causes of death that year, a tumor mortality of $1.6:1,000$ might

still not have been observed, because younger age groups made for a larger proportion of the Swedish population at that time than in 1950. Calculating with a conjectured tumor death rate of 1.4 yields 3 annual deaths from angioblastomas in a population of 5.7 millions, which, in a population of 7 millions, corresponds to 4 annual deaths.

In *Lindau's* series [1926] 8 patients with untreated angioblastomas of the cerebellum had had symptoms from 5 months to 6 years before death, on an average 19 months. *Olivecrona* [1952] observed that the length of history before admission varied between a few weeks up to 2 years, about two thirds of his patients came under neurosurgical care within a year of the appearance of the first symptoms.

If survival in untreated cases amounted to 2 years, then, according to the foregoing rough guess, 8 annual cases of clinically manifest angioblastomas would occur in the present population. A survival of 1 year, on the other hand, would correspond to 4 annual cases.

From *Olivecrona's* operated series [1950, 1955] an annual average of 4 angioblastomas can be calculated to have been observed. In the Neurosurgical Clinic of Lund, with an admission area inhabited by 1.8 million people [1954], 19 histologically verified angioblastomas were observed in the years 1946 to 1955, i.e. an annual observation rate of 2 cases (by courtesy of Dr. *N. Lundberg*).

Cerebellar angioblastomas give rise to a series of dramatic and characteristic symptoms and signs. It can be assumed, therefore, that the major part of clinically manifest cerebellar angiomas are detected and treated surgically. Then about 6 annual operations for cerebellar angiomas would represent an acceptable estimate of the incidence of such tumors. It tallies with the foregoing conjecture of 4 to 8 annual cases. The incidence rate of symptom-giving angioblastomas may be somewhat higher than the annual average of surgically verified cases, perhaps at most twice that average.

In several families capillary angiomas of the central nervous system have been observed in both sexes of successive generations (*Rochat* [1927]; *Möller* [1929, 1944]; *Fraccaro, Maggi and Mariani* [1954]; *Silver* [1954]; review in *Zülch* [1956]). The cited authors, and others, have published pedigree charts which are in accord with inheritance of angiomatosis as due to a rare, autosomal, dominant gene. The same was the case with a South Swedish family, where the proband was described as Case 2 in *Lindau's* publication of 1927. The son of that proband developed retinal angiomatosis and was blind several years before he died from a tumor of the medulla oblongata and cerebellum. Histologic proof was not available,

but clinical data, including gross appearance of the inoperable tumor, were suggestive of angiomatosis.

Though generalized conclusions cannot be drawn from pedigrees selected for multiple occurrence of the disease, it is notable that observations suggestive of other modes of inheritance are absent. If some angioblastomas were due to a rare, recessive gene, reports on consanguineous parentage could be expected in such cases. However, the only case of parental consanguinity in angiomatosis that has been published seems to be case 15 in *Lindau's* study [1926].

Clinically manifest angiomatosis of the central nervous system is a rare disease. If all cases were due to inheritance of an autosomal, dominant gene, a few hundred carriers of that gene would occur in the Swedish population. Even if not excluded, the homozygous state could hardly be expected to be observed.

Olivecrona [1952, 1954] observed angiomatosis in 2 or more members of three families, one of them was also studied by *Sæbø* [1952]. The fact that only three angioma families were met with in *Olivecrona's* operation series of 70 cases may be partly explained by smallness of sibships and relatively late manifestation, tending to reduce the chance of secondary observations in such families.

In a series of 19 histologically verified (*Lindau*) angioblastomas from the Neurosurgical Clinic in Lund, 14 patients were men, 5 women. The age of onset of clinical symptoms varied from 17 to 61 years, the mean age was 42 years. The duration of symptoms before operation was, for 17 patients, 8 months. Of 19 patients 5 have not married, 13 of 14 married patients have children. The average number of children was: for 13 married patients, 2.7; for the whole series of patients $35:19 = 1.8$.

These crude figures seem not to necessitate the assumption of a high mutation rate to explain the persistence of the disease in the population.

In the series under study no verified angiomatosis has been observed in 63 sibs of 11 patients with cerebellar angiomas. Among 53 children of sibs of 9 patients 2 girls had cutaneous hemangiomas, requiring radiologic treatment, and one woman had palatoschisis, she died from a medulloblastoma at the base of the fourth ventricle. A man, first cousin of a patient with cerebellar angioma, had a cerebellopontine angle meningioma.

During a prolonged time of observation, as in the study by *Möller* [1929, 1944], a greater proportion of sibs and children of probands arrive at the age of manifestation of angiomatosis. It is possible that such studies, by time and patience, of unselected families may reduce the proportion of angiomas of the central nervous system that seem to arise sporadically.

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HEREDOPATHIA ATACTICA POLYNEURITIFORMIS

By S. REFSUM

A neurological syndrome, of hereditary nature, first termed heredo-ataxia hemeralopica polyneuritiformis, was described in 1945 [7, 8], and later termed heredopathia atactica polyneuritiformis [9, 10]. The first term gave an indication of some of the outstanding clinical features of the syndrome, but the latter, more neutral term was preferred because there was no pathological proof at that time of its relationship to the heredo-ataxias.

On the contrary, *Cammermeyer* based on his preliminary pathological studies of two of the cases suggested that the syndrome might belong to the lipoidoses. From a purely clinical standpoint, however, this has always seemed less probable to me. This syndrome is characterized by an atypical retinitis pigmentosa with night-blindness and a concentric constriction of the visual field; a chronic polyneuritis-like picture with progressive pareses of the distal parts of the limbs; decreased or absent deep reflexes; ataxia

and other cerebellar signs; increase of the protein content of the cerebrospinal fluid with normal cell count and electrocardiographic changes in most of the cases; and also, in some cases, diminution of hearing of a neurogenic type, pupillary abnormalities, symmetrical epiphyseal dysplasia in the elbow, shoulder and knee joints and ichthyosis-like skin changes. Sudden death has occurred in several cases.

The clinical analysis indicated that the syndrome might be related to the heredo-ataxia group, particularly the *Friedreich* type, with points of similarity also to progressive neurospinal amyotrophies (of the *Charcot-Marie-Tooth* or the *Déjerine-Sottas* type). As to the possibility of a relationship of this syndrome to the lipoidoses, it was emphasized that not one of these patients showed signs of mental deterioration or definite oligophrenia. In the available literature no report had to my knowledge previously been given of cases with this particular combination of symptoms and signs.

The syndrome was first observed in a brother and a sister whose parents were first cousins. Shortly after, it was observed in two patients who were first cousins in a family unrelated to my first cases. The parents of both these patients were second cousins. (Fig.) A sister of one of them had presented the same clinical picture and died suddenly while she was sitting in the waiting room of an eye clinic. Later two additional cases have been observed in our second family group which brings the number of patients in this family up to five.

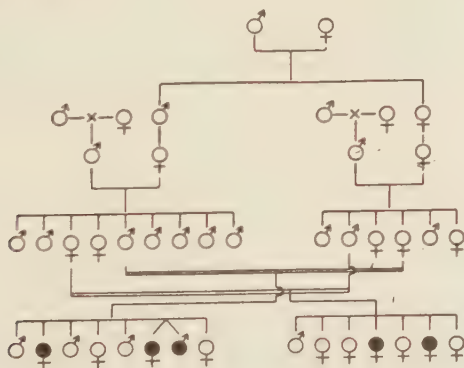


Fig. 1. "Family B". Black symbols indicate the affected members of the family. The parents of the patients are second cousins.

The age of onset in all these cases was the second and third decade. In 1949 the same neurological syndrome was diagnosed in four children,

where it had started between the ages of 4 and 7 [11]. This brings the total number of personal cases up to eleven. These four children belonged to three mutually unrelated families which were also unrelated to the adult cases originally observed. Three of these children stemmed from consanguineous marriages.

The occurrence of this syndrome has not been limited to Norway. One case has been reported by *Reese* and *Bareta* in 1950 from United States [6] and Dr. *Reese* told me that he has seen one more case in a second family. Another case has been observed by *Clark* and *Critchley* in England [4]. From Sweden the syndrome has been reported by *Kjellson* in 1953 [5] in a brother and a sister whose parents were first cousins.

It seems reasonably well established that we are dealing with a circumscribed and well characterized clinical syndrome of an hereditary nature.

Regarding pathology there are now 6 autopsied cases. The first 4 are from Norway; the 5th, from the USA, was studied by *Reese* and *Bareta*, and the last, from Sweden, reported by *Kjellson*, was studied by *Gellerstedt*.

Reese and *Bareta* from their case concluded that the syndrome belongs in "the complex group of interstitial hypertrophic polyneuritis". *Gellerstedt* found, as *Cammermeyer* had previously reported, degeneration of nuclei and fiber tracts in the brain stem, particularly within the rubro dentate system and in the olivopontocerebellar tracts. He denied, however, that a lipoidosis was responsible for the changes in the central nervous system.

In a paper at the meeting of the American Association of Pathologists in 1954 by *Cammermeyer* and *Haymaker* [3] the conclusion was that the peripheral nervous system of 3 of our cases and the 4th reported by *Reese* and *Bareta* showed the complex of changes characteristic of hypertrophic interstitial polyneuritis and that the syndrome belongs in the group of neuro-muscular disease, of which other variants are those described by *Friedreich*, *Charcot* and *Marie*, *Déjerine* and *Sottas*, and others.

Finally, as to the genetic aspect the parents of all patients reported by us and by other observers were blood relatives, with only one exception. In all families the parents were unaffected by the disease. This is strong evidence in favor of recessive heredity. A small and selected material like the one at hand is not suitable for any attempts at a statistical analysis. However, no observations seem to contradict the hypothesis originally maintained that the syndrome is caused by a single autosomal recessive gene.

The name of the syndrome is long and difficult. It has already been changed once by myself. Dr. *Joe R. Brown* in his chapter in *Baker's* handbook, *Clinical Neurology*, termed it "polyneuritic (hereditary) spino-

cerebellar ataxia". I dislike the idea of changing it once more. If I had known when I termed the syndrome what the neuropathologists now have told me, I would have preferred to use the name heredoataxia polyneuritiformis.

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A CLINICAL AND GENETIC STUDY ON TREMOR ESSENTIALIS IN A NORTH- SWEDISH POPULATION

By T. SJÖGREN

Will be published later as a monograph.

Gouda, Holland

HEREDITARY CONGENITAL FACIAL PARALYSIS

By H. J. VAN DER WIEL

A family is described with a congenital palsy of the n. facialis, in most cases bilateral, sometimes as a "forme fruste". The disease was manifest in 6 generations; 14 affected parents have 70 children, 32 of which were also affected. The sex-ratio was 1:1. None of the affected siblings showed any other neurological symptoms. The pedigree suggests an autosomal, irregular dominant, monomer gene. Unfortunately no histo-pathological investigations could be made; it seems probable, however, that the disease must be considered a monosymptomatic form of Moebius' Kern-aplasia.

Will be published in: *Folia Psychiatrica Neurologica et Neurochirurgia Neerlandica*.

Discussion

J. G. Y. de Jong (Heerlen): Did you find any signs of hyperacusis or signs of affection of the chorda tympani, or disturbances of taste?

H. J. van der Wiel (Gouda): No, there was no hyperacusis and the eighth nerve was always normal, as was the taste.

HEREDITARY FACTORS IN ENDOGENOUS PSYCHOSES

Lewis, A. J.: Acta genet. 7, 349-365, 1957

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THE OFFSPRING OF PARENTS BOTH MENTALLY ILL

By A. J. LEWIS

I present this brief paper diffidently, because of the lapse of time—over 20 years—since the material was obtained.

In 1932 I began to collect information about patients who showed “conjugal psychoses” and about their offspring. The offspring, however, were in so many instances still young that I thought no statistical ledger-domain could be a substitute for patience and complete data such as might be obtained by waiting another ten years, i.e. until 1943, then re-establishing contact with the offspring; and if necessary repeating the process in 1953, by which time almost all the children would have passed the age of risk. However I reckoned without my host: in 1943 we were all otherwise engaged and when I tried to pick up the threads, more recently, I found that in the interval the disruption of communities because of bombing and movements of population, had put it out of my power to find the people again. Searching the central register of all persons admitted to the mental hospitals of England and Wales presented another possible way of discovering the psychotic offspring, but women who had married in the ensuing twenty odd years were untraceable because of the change of surname, and there were other technical difficulties in identifying individuals.

It was plain that the material must be presented as it was in 1933, or not at all. The publication in 1952 of Professor *Elsaesser's* monograph suggested that even a small further series deserved to be put on record.

The method of collecting the parents was based on a large card-index at the Maudsley Hospital, compiled at the instance of the late Sir *Frederick Mott*. *Mott*, deeply interested in the heredity of mental disease, persuaded the doctors of the London County Asylums to send him details of every

instance in which a patient admitted to their mental hospital already had another member of his family in a London County Asylum. The system was introduced in 1908, and by 1932, when I wanted to use it, the register was very extensive. The doctors had interpreted Mott's request literally, and had therefore included husbands and wives as members of the same family, though *Mott* had not intended them to do so, wanting only parent and child, sibs, and collateral relatives. The nature of the relationship was always specified, and by going through all the cards I was able to extract the names of 384 husbands and wives (192 couples). The earliest date of admission was in 1862 and the latest 1931. Although many of the patients had blood-relatives also recorded in one of the London Asylums, there is no reason to suspect that this influenced the inclusion of the husbands and wives; certainly the existence of any psychotic offspring of such couples was so rare an entry on the cards that it could not have played any part in the selection. We had therefore a pretty clean sample of "conjugal psychoses" reported in the London Asylums (which at that time had in all about 20,000 beds).

Scrutiny of the case records of the 384 patients showed that in 71 couples one or both of the partners had been affected with G.P.I. These were investigated separately, to discover how many of the surviving children had developed neurosyphilis: but I shall not say anything more of these. The offspring of the remaining 121 couples were then searched for, using their original addresses and the addresses of their relatives during the time the patients were in the mental hospital. Bearing in mind the length of time that had elapsed in most cases, the mobility of an urban population and the particular factors favouring the dispersal of families so drastically affected, it is obvious that tracking the offspring down was a most elaborate and often baffling business. In many instances it necessitated visiting eight or nine addresses in widely dispersed areas, searching nominal rolls, and so forth. This skilled and exacting work was carried out by Mrs. Janet *Jackson*, a psychiatric social worker who succeeded remarkably in what is surely one of the most delicate field-inquiries that can be undertaken—a complete stranger calling on the children of parents who have both been insane, explaining to them the reason for the visit which recalls painful memories and personal fears, and then inquiring into their own lives and the mental health of their brothers and sisters. This Mrs. *Jackson* accomplished with such tact and sympathy that many of those whom she had approached wrote appreciatively to her afterwards or invited her to come again: she found that "those who felt secure in themselves were co-operative because of their security, and those who dreaded the possibility

of such trouble (psychosis) in their own cases were often expansive, glad to talk over their anxiety with an impartial stranger”.

Twelve of the couples had had no offspring; others had had children who died before the age of 20 or had not reached that age by the time the investigation was made. These couples were excluded from the inquiry, as were also couples one or both of whom had had epilepsy, senile or arteriosclerotic dementia or other organic disease causing the initial psychosis for which the patient had been admitted to the mental hospital. When these couples had been eliminated, together with those who could not be traced, we were left with 40 couples who had at least one child over the age of 20.

For these 40 couples there were 143 children who had survived until over 20. Nine of the children had passed the age of 60; four were over 70.

Whenever it was known that one of the offspring had been in a mental hospital his case records were of course obtained; any of the offspring not in a mental hospital who showed symptoms suggesting abnormal personality or neurotic or other mental disorder, was seen by me, if he would consent to this.

The diagnosis of the parents' illnesses presented great difficulties. Some of these are common to all family studies; others arose from the special circumstances of this inquiry, depending as it did on the clinical records of London mental hospitals during a period roughly covering the last quarter of the 19th century and the first quarter of the 20th. During that period the terminology and the classificatory outlook prevailing among doctors in English mental hospitals was remote from that now employed: it is therefore impossible to use the diagnoses made by those who knew the patients well, and hazardous to attempt to rediagnose the patient's illnesses in current or Kraepelinian terms. However it had to be done. Like others, I have had special doubts about what to do with involuntional melancholia, with the late-appearing paraphrenic forms, and the chronic paranoid psychosis that supervenes on an acute alcoholic hallucinosis. The form and course of the illness rather than its origins or age of onset, or the illnesses of the patient's relatives, have been what I relied on: and in consequence I have usually reckoned the involuntional depressions with the affective group, and the paranoid conditions just referred to with the schizophrenias: atypical conditions were distinguished from unequivocal ones, and when both schizophrenic and affective features were equally prominent, I have allowed the course of the illness to decide in which category to place it. As my material is small I have made no further subdivision, such as *Schulz* used. The clinical records on which any diagnosis must be based in these

cases are so defective for the purpose that it would be futile and misleading to try to squeeze inferences out of them by refined analysis or casuistry.

Table 1. Number of parental couples with endogenous psychoses

	<i>Schulz</i>	<i>Elsaesser</i>	<i>Lewis</i>
Schizophrenia × Schizophrenia	20	14	4
Affective Psychosis × Affective Psychosis	17	4	5
Affective Psychosis × Schizophrenia	15	4	7
Atypical Endogenous Psychosis in one or both Parents	45	15	24
	97	37	40

If it seems that my series is of a respectable size, on the whole, when set alongside Professor *Elsaesser's* or even Dr. *Schulz's*, I must emphasize that the amount of information I collected about the subjects was much less than they were able to accumulate on their families.

Among the offspring, those who had had signs of mental disturbance without having been admitted to a mental hospital for it, were a further diagnostic problem. In many cases the amount of information about them was enough to raise a doubt, but not enough to resolve it. There is, of course, much to be said in favour of including, for example, brief or mild hypomanic and depressive illnesses in the same category as the manic-depressive illnesses necessitating mental hospital care. If, however, a similar principle were adopted in respect of parents, age of onset in many of them would be pushed back twenty or thirty years: much larger collections of "conjugal psychoses" could be made, but the comparability of different investigators' findings would become much lower than at present.

In this series, therefore, for practical reasons those children who have had treatment in a mental hospital are dealt with separately and called "psychotic". Those whose disturbances of personality and behaviour have been dealt with at general hospitals, outpatient departments, or by general practitioners are listed apart from the "psychotic", even though their illnesses may have clearly belonged to the schizophrenic or affective category. The reasons for this do not derive from belief in a distinction between neurotic or "psychogenic" disorders on the one hand, and "constitutional" or psychotic ones on the other, but from the practical need to have an arbitrary definition of a "case". Also for practical reasons, the reported occurrence of ulcerative colitis, asthma and other "psychosomatic" illness

in some of the children has not been included: the information is too meagre and inexact to warrant its use.

To calculate the proportion of children who are affected among those exposed to risk, I have used the shorter Weinberg procedure, taking twenty years as the lower limit of the period of risk, and fifty years as the upper limit. I have reckoned every psychotic child as one, irrespective of his age; and I have throughout taken age as being age at death, or at latest period for which information is available. The upper limit of 50 was taken for this calculation, in all cases, without regard to whether the parents were schizophrenic or manic-depressive, for the following reasons: the age of onset of the first attack is higher in this material than in a representative sample of all schizophrenic or manic-depressive persons: it is impossible when one parent is manic-depressive and the other schizophrenic, to arrive at a corrected figure for children at risk which would discriminate in respect of upper limit between those who might become schizophrenic and those in danger of affective psychosis; the Strömgren and the Slater devices for calculating the Bezugsziffer seem unnecessary for such small numbers. It is worth noting moreover that in Slater's twins and their relatives he found that as many as 20 per cent of his schizophrenic subjects had first fallen ill after the age of 40; indeed 6 per cent had first fallen ill after the age of 50. Similarly more than half of his subjects with affective illness had not broken down until after the age of 40.

I must return to the age of onset in the parents: it was high. The figure given is that at which indubitable signs of psychosis appeared. Often the record showed that mental abnormality had been evident for years before this but was disregarded because inconspicuous or insidious. In others this was not the first attack, but the first to require mental hospital admission. In many of the illnesses classed as affective, beginning in the fifties or sixties, the patient had been discharged "recovered", and in several of them was known to have been free from illness for up to 15 years subsequently. When there was serious room for doubt regarding the presence of arteriosclerotic, presenile or senile or other cerebral disease, the pair in question were eliminated from the study, though dementia supervening after, say, ten or fifteen years in the mental hospital was not taken as a ground for exclusion.

Reports of family and twin studies, including Dr. Schulz's and Dr. Elsaesser's reports on the offspring of psychotic pairs have usually included detailed clinical accounts of the persons dealt with in the inquiry, so that others could reconsider the diagnosis, if they wished: and the authors have usually been driven to rather anguished acknowledgment of the mis-

givings they had felt about the diagnosis in particular instances, and the straits to which they had been put in making up their minds about it. This report is no exception: and I put the tables forward with no claim for diagnostic certitude, though in the psychotic children I have not experienced as a rule any serious difficulty in deciding on the diagnosis, chiefly because the hospital records were much fuller and more satisfactory for the purpose.

Table 2. Children of parents with typical schizophrenia.

Parental Pair	Age of Onset	Children	Corrected Children at Risk	Psychotic Children	Diagnosis of these	Age of Onset	Other Children Affected	Diagnosis of these	Total Children Affected
N. E.	25, 28	2	2	1	Schizophrenia	26	1	Obsessional attacks with depression	2
W. H.	40, 44	2	0.5	—	—	—	—	—	—
W. M. S.	33, 23	3	1.5	—	—	—	—	—	—
W. G. W.	29, 48	5	4.5	2	1. Schizophrenia 2. Schizophrenia	39 26	1	Paranoid psychopath	3
4		12	8.5	3			2		5

Table 3. Children of parents with atypical schizophrenia.

Parental Pair	Age of Onset	Children	Corrected Children at Risk	Psychotic Children	Diagnosis of these	Age of Onset	Other Children Affected	Diagnoses of these	Total Children Affected
C. C.	43, 44	5	3.5	—	—	—	—	—	—
J. L.	31, 40	2	1	—	—	—	—	—	—
H. P.	42, 41	8	4.5	1	Schizophrenia	22	1	Severe reactive depression with paranoid features	2
3		15	9	1			1		2

Schizophrenic parents. Schulz estimated the probability of schizophrenia in the offspring of schizophrenic parents at 41 per cent if both

parents had the disease in typical form, at 30 per cent if one of them had it in atypical or doubtful form. The atypical forms in my series included a husband and wife (C. C.), both aged 44, who were admitted to hospital on the same day in 1906. The wife had belonged to a very narrow sect; both she and her husband had been extremely religious during the twenty years of their married life. Two and a half years before admission, God began to speak to them both. Towards the end of 1904 they burnt their furniture, on divine instructions, and in 1905 God spoke to the husband ordering him to throw up his work and prepare for a special mission. During the ensuing twelve months they remained strictly within their house, reading the Bible and praying, and waiting to be taken bodily to heaven. The Lord spoke to them daily and appeared to the wife in visions. On admission the husband expressed many delusions about his divine mission, said God had thrown him to the floor on one occasion, and constantly spoken to him. He charged his neighbours and his sons (who had supported him during the twelve months he stayed away from work) with plotting against him. The wife told of the same beliefs and experiences—visions, God's voice which had to be obeyed, promises of being taken up into Heaven. She improved and recovered insight faster than her husband: she said her messages had begun at an earlier date than her husband's, but that she had been influenced by him. He too improved, but had a relapse: he was not able to leave hospital until after 10 months—his wife left after six months. (This pair is rather like the pair IV-16 in Schulz's series of "querulants and induced insanity", and reminiscent also of his pairs IV-5, IV-7, and IV-17; but there are also considerable differences.)

In another pair (J. L.), the husband had a gross catatonic schizophrenia (punctuated with outbursts of excitement) which lasted from his admission in 1906 till his death in the mental hospital in 1936. His wife was admitted in December 1912: she was much undernourished, having had great difficulty in supporting her two children since her husband went to hospital. She was said to have starved herself to feed the children and pay the rent. She also had a mitral lesion, was quite deaf and nearly blind: she had had a double iridectomy. On admission, she believed she was receiving messages through a spirit and that blood gushed from her fingers carrying her secrets with it. There was much evidence of thought disorder of the schizophrenic type. She had auditory hallucinations, said the spirits of all her relatives were passing through her body, and talked to herself constantly. After she had been five years in the mental hospital, isolated by her deafness and blindness, but sometimes quarrelling and fighting with other patients, she was taken out by her mother but subsequently had to

be readmitted. Subsequent notes record her profound depression, her fights with other patients, hypochondriacal complaints and "answering the voices all day long". She died in hospital in 1941. It is clearly impossible retrospectively to judge how far deafness, blindness and malnutrition contributed to the clinical picture, and the classification as "atypical schizophrenia" could be questioned.

The relation of type of mental illness in the offspring to that in the parents is illustrated by the third pair in the atypical schizophrenic group (H. P.). The husband was admitted to hospital in 1913, with many paranoid delusions—his wife was conspiring with his neighbours to flick pepper into his eyes, the authorities at the Infirmary had tried to murder him by poisoning his food, and so forth. He continued, without much recorded change in his mental state, during the next ten years, and was thought by the doctors who looked after him to be becoming demented. However in 1923 he escaped from the mental hospital and, though he remained hallucinated and muddled, he picked up the threads of his normal life sufficiently, and nine years later was still at home. His wife was first admitted to a mental hospital in 1903, with auditory hallucinations and beliefs that she was being poisoned and defrauded, chiefly by her husband. She improved, but was still prone to laugh incongruously and express far-fetched ideas, when her husband took her out of hospital "not improved" four months after admission. In 1927 she was readmitted, expressing much the same delusions as a quarter of a century earlier—her food was being poisoned, her husband had marked her for death. She said she was older than the Virgin Mary, she misidentified people, and she asserted she was pregnant. She remained in the hospital until her death in 1938: latterly she had occasional fits, probably uraemic, and became demented. The eldest son of this pair was admitted to a mental hospital in 1910, when he was 22. He showed many catatonic features and heard voices telling him he was wicked. He was in a semi-stupor for about a year after admission, he gradually emerged from this, becoming abusive, grimacing and performing antics. He believed his thoughts were read, and that he was being persecuted. From 1914 onwards he was rather more in touch but was considered to show much deterioration. His father took him out of hospital in 1923 (shortly after his own escape!) and the patient remained at home for the next nine years, unoccupied, refusing to get up or wash, and threatening to kill his sister, who looked after the house.

There are similarities here between father and son, but differences in form are also striking: the father's illness was throughout paranoid, the son's catatonic in the main: and the mother's, likewise paranoid, was in

the first instance episodic. The prospect of elucidating genetically distinct clinical forms by scrutiny of individuals such as these, is not encouraging.

Table 4. Children of parents with typical affective psychosis

Parental Pair	Age of Onset	Child- ren	Corrected Children at Risk	Psych- otic Children	Diagnosis of these	Age of Onset	Other Children Affected	Diagnosis of these	Total Children Affected
H. A.	57, 46	3	1.5	—	—	—	2	1. Depression 2. Depression	2
C. H.	55, 52	1	1	1	Recurrent depression	26	—	—	1
J. W.	65, 30	5	3.5	1	Melancholia	30	—	—	1
J. E.	26, 35	7	4	1	Paranoid schizo- phrenia: alcoholic	33	3	1. Anxiety neurosis 2. Alcoholism 3. Alcoholism	4
T. D.	42, 58	6	5.5	3	1. Recurrent depression 2. Recurrent excitement (mania) 3. Depres- sion: suicide	16 18 42	2	1. Puerperal delirium 2. Alcoholism	5
5		22	15.5	6			7		13

Parents with affective psychoses. In these the preponderance of conditions developing after 50 is obvious. As *Schulz* and *Elsaesser* so emphatically pointed out, this is perhaps undesirable, but it cannot be helped. *Elsaesser* computed that if these and the moderately atypical forms of affective psychosis are excluded from the series, hardly any cases would be left. “Dass ich die Fälle mit leichten Atypien und die erst im Alter beginnenden manisch-depressiven Psychosen mit zu dem Kreis des eigentlichen MDI hinzugenommen habe ist schon eine Kompromißlösung, um überhaupt eine Berechnung von Belastungsziffern zu ermöglichen. Das ganze manisch-depressive Material wäre ja sonst auf 4 Elternpaare von Schulz und ein eigenes Paar zusammengeschrumpft.”

It is necessary to look at those affective pairs who had a child with a non-affective psychosis. The first of these was a pair (J. E.) of whom the father, first ill at age of 26 with mania, had recurrent mania until his death at the age of 66, and the mother had an attack at 35 of acute self-reproach-

Table 5. Children of parents with atypical affective psychosis

Parental Pair	Age of Onset	Children	Corrected Children at Risk	Psychotic Children	Diagnosis of these	Age of Onset	Other Children Affected	Diagnosis of these	Total Children Affected
C. A.	57, 35	5	3	(1)	G. P. I. (expansive)	40	1	Depression	2
F. C.	48, 31	1	0.5	—	—	—	—	—	—
D. E.	62, 58	4	2	—	—	—	1	Obsessional neurosis with depressive phases	1
A. F.	54, 22	2	2	—	—	—	—	—	—
F. H. M.	55, 33	8	4.5	—	—	—	2	1. Menopausal depression 2. Depression	2
W. N.	44, 51	3	3	2	1. Paranoid Schizo- phrenia 2. Senile Paraphrenia	58 67	—	—	2
J. N.	31, 59	1	1	1	Melancholia	58	—	—	1
R. A. R.	18, 33	1	0.5	—	—	—	1	Sexual crimes: psychopathic personality	1
W. A. M.	60, 59	7	4	1	Depression	27	2	1. Dull and backward 1. Anxiety since meningitis	3
W. P.	32, 21	1	0.5	—	—	—	—	—	—
10		33	21	5			7		12

ful depression, from which she recovered after three months in hospital. The eldest son had been steadily working for the same firm for 15 years prior to his breakdown: he had, however, been drinking ale to excess, in periodic bouts. At the age of 33 he became convinced people were following him about, talking about him and spying on him: he felt they were putting electrical influences on him: he had auditory hallucinations and was excited. He was admitted to a mental hospital, where he remained for 8 months, with gradual improvement. On discharge he obtained work in a paint firm where he remained for 11 years, but developed lead-poisoning and had to leave. For the next six years he was unemployed and subject

to spells of mild depression which he coped with without medical aid. Obviously alcohol was an important cause of the transient paranoid condition, which could alternatively be regarded as an alcoholic hallucinosis in a person of depressive temperament.

The child with G. P. I. need not detain us (C. A.). Another affective pair presented atypical features and had two paraphrenic sons. The father had a manic attack in 1862, at the age of 44, from which he never fully recovered, though when he seemed well he was discharged from hospital: he could remain out, however, only a very short time. He died in hospital at the age of 85, after 40 years of "chronic mania". His wife at 51 became morose, refused to eat, wanted to cut her throat and was convinced that her daughter who died in childbed had been poisoned. While in the mental hospital (1873-1885) she wept a great deal, and said she would like to be burned to death. She also believed that people were against her, and at times abused the nurses and doctors, believing they were her enemies. She became as the years went by actively hostile towards anyone who

Table 6. Children of a parent with typical schizophrenia and a parent with typical affective psychosis.

Parental Pair	Age of Onset	Children	Corrected Children at Risk	Psychotic Children	Diagnosis of these	Age of Onset	Other Children Affected	Diagnosis of these	Total Children Affected
G. F. A.	39, 50	4	3	2	1. Depression: Suicide 2. Depression: Suicide	21 24	1	Puerperal depression	3
E. J. A.	32, 36	2	1	—	—	—	1	Cyclothymia	1
W. G. A.	34, 43	4	2.5	1	Depression	19	3	1. Hypomania 2. Hypomania 3. Depression	4
A. A.	52, 43	2	1	—	—	—	1	Reactive depression	1
H. R. H.	34, 45	6	2.5	1	Schizophrenia	31	2	1. Morbid jealousy 2. Violent rages	3
M. M.	37, 50	3	2	1	Schizophrenia	26	—	—	1
J. W.	37, 62	5	3.5	—	—	—	1	Alcoholism	1
7		26	15.5	5			9		14

Table 7. Children of a parent with atypical schizophrenia and a parent with typical affective psychosis.

Parental Pair	Age of Onset	Children	Corrected Children at Risk	Psychotic Children	Diagnosis of these	Age of Onset	Other Children Affected	Diagnosis of these	Total Children Affected
C. G.	51, 69	2	1.5	—	—	—	—	—	—
D. W. P.	39, 24	4	2	—	—	—	—	—	—
G. P.	58, 52	6	2.5	1	Chronic Melancholia: Manic phase: infanticide	25	—	—	—
3		12	6	1			—		1

Table 8. Children of a parent with typical schizophrenia and a parent with atypical affective psychosis.

Parental Pair	Age of Onset	Children	Corrected Children at Risk	Psychotic Children	Diagnosis of these	Age of Onset	Other Children Affected	Diagnosis of these	Total Children Affected
T. B. D.	38, 49	5	2.5	—	—	—	2	1. Violent rages 2. Depression	2
F. V. H.	36, 35	1	1	1	Schizophrenia	22	—	—	1
2		6	3.5	1		2			3

approached her, and during the last few years of her life was solitary, silent and resentful of any intrusion. The eldest son was free from mental illness until the age of 58: he then became agitated and preoccupied with paranoid delusions and after admission to the asylum he came to believe he owned it and had been put in it by the Royal Family. He gradually deteriorated and died after eleven years in the mental hospital. His brother had a similar illness, coming on at 67, necessitating admission to a mental hospital and lasting until the end of his life more than nine years later. It is arguable that these paranoid psychoses coming on in late life, in the setting of severe agitation and excitement, are closer to involutional melancholia than to paranoid schizophrenia: but, in any case, the similarity in form and course between the psychoses of the parents and the offspring here is striking.

Table 9. Children of a parent with atypical schizophrenia and a parent with atypical affective psychosis.

Parental Pair	Age of Onset	Children	Corrected Children at Risk	Psychotic Children	Diagnosis of these	Age of Onset	Other Children Affected	Diagnosis of these	Total Children Affected
J. T. L.	38, 27	3	1	—	—	—	2	1. Depression 2. Depression (recurrent)	2
A. M.	47, 44	6	2	—	—	—	1	Depression	1
T. S.	29, 36	3	1.5	—	—	—	1	Excitable psychopathic personality	1
R. J. W.	60, 55	6	3.5	1	Depression: Suicide	23	4	1. Alcoholism 2. Anxiety neurosis; alcoholism 3. Anxiety neurosis 4. Unstable psychopathic personality	5
T. W.	61, 62	5	3.5	—	—	—	1	Alcoholism	1
G. T. C.	52, 62	4	2.5	1	Schizophrenia	24	1	Reactive depression	2
6		27	14	2			10		12

Mixed pairs. These may be compared with *Schulz's* 30 mixed pairs, reported in November 1940. He pointed out the objections to assuming that it is from such marriages that schizo-affective forms could arise, and he left open the question whether the findings ran counter to his suggestion that there is a common genetic determinant for all endogenous psychosis, and that it is an additional "releasing" factor which determines whether the psychosis shall be schizophrenic or affective. My material is of course too small to be trusted, but the findings do not lend support to *Schulz's* suggestion; they accord with *Elsaesser's* on this point.

The proportion of affected children in each group is lower than in *Schulz* and *Elsaesser's* series, but high enough to confirm the generally accepted opinion about the inheritable character of these "endogenous psychoses". The smaller proportions I obtained may be due to diagnostic bias, leading me to include as "endogenous psychoses" conditions in older parents which others would list separately or exclude, or it may be due

Table 10. Summary of affected children from various combinations of parental psychosis.

Mating	Number of Pairs	Corrected Number of Children at Risk	Psychotic Children		Other Children Psychiatrically Abnormal
			Schizophrenic	Affective	
S × S	4	8.5	3	—	2
? S × S	3	9	1	—	1
A × A	5	15.5	1	5	7
? A × A	10	21	2	2	8
A × S	7	15.5	2	3	9
A × ? S	3	6	—	1	—
? A × S	2	3.5	1	—	2
? A × ? S	6	14	1	1	10
	40	93	11	12	39

(S = schizophrenic, A = affective, ? = atypical.)

to different practices in regard to mental hospital admission in England and Germany during the periods covered. If the children with psychiatric abnormality, who were not treated for it in a mental hospital, are included, the proportions are appreciably raised. This would accord with *Leonhard's* proposal that manic-depressive parents dealt with elsewhere than in mental hospitals should be specially sought for; and the same might be said of the offspring.

There are two matters on which this type of study might be expected to throw light: the genetic identity of the clinically recognized "endogenous" psychoses, and mode of transmission. The data in this little series can hardly be said to throw light: at most they contribute a feeble taper to the wavering glimmer in which we view these vexed questions. They confirm the similarity of the psychoses of children with those of their parents; but they lend no clear support to the assumption that schizophrenia is attributable to a specific recessive gene, nor indeed to any of the more complicated explanations that have been put forward, touching on the influence of the "genotypic milieu", the postnatal environment, and so forth. As *Elsaesser* rightly says on this question: "Bei dem relativ kleinen Ausgangsmaterial (ist) eine Zufallsschwankung nicht ausgeschlossen... Wenn wir nach den zur Zeit stark vertretenen Hypothesen eine rezessive Erbweise der Schizophrenie und eine dominante Erbweise des MDI annehmen, so müßten wir ja überdies sogar mehr kranke Kinder bei den Schizophrenen als bei den manisch-depressiven Elternpaaren erwarten.

Die Erbgänge der großen Psychosen sind jedoch noch so wenig bekannt, daß diese Überlegung uns in keiner Weise weiter helfen kann."

I said at the beginning that I present this material with diffidence. The first reason for my diffidence is the long interval that has elapsed since the data were collected. A second reason is the doubt I have whether the findings can be trusted. The grounds for this misgiving will have been mostly evident in what I have said already. May I briefly recapitulate them. First: the selection of the sample. Even if, as in the series, it is unbiassed by any awareness on the selector's part of illness in the offspring of the affected couples, the sample will still be restricted to fertile couples; yet people who became ill before they had procreated or whose children died young may have suffered from specially severe forms of mental illness with a stronger likelihood of manifestation and other genetic features. Moreover any such sample of parents will contain a higher proportion of patients whose illness began in middle life and later, than would be found in the whole population of persons with the relevant "non-organic" illness.

Secondly: the ascertainment of the offspring is a difficult task. Inevitably many persons are lost through emigration and failure to trace their address.

When both parents have been psychotic, possibly spending the last twenty or thirty years of their lives in the mental hospital, the family will have been disrupted and finding them is exceptionally difficult; some of the children, moreover, will have been taken over or adopted by relatives whose name the child thereafter goes by. Illegitimacy has also been a minor problem in our series. The central register of mental hospital admissions, though a help in tracing some affected children, is of little use—at any rate in England—in finding people who have common surnames, or whose age and full Christian names are not precisely known. It cannot help, either, in finding offspring with psychiatric illness that has not been treated in a mental hospital—psychopathic personality, neuroses and crime are outside its range. (I had one instance of a woman who had attempted suicide and at the same time murdered her child, but because Broadmoor, the State Criminal Asylum, was at that time regarded as part of the Prison Service and not of the Mental Hospital Service, she did not appear in the central register.)

Personal visits are therefore essential for this study, but in England, at any rate, they require an enormous amount of effort and time; and they often expose both the investigator and the investigated persons to an emotional strain which is justified only if the results are of commensurate importance: I am inclined to think they are not.

Moreover, the offspring had to be investigated at a time when many of them were still open to the risk of developing a mental illness later on. None of the devices for getting round this familiar obstacle seems to me satisfactory in the kind of family study we are considering, chiefly because we are ignorant of the genetic relations between parents and child in respect of age of onset of illness, especially when the two parents differ in type and course of illness.

Thirdly: diagnosis is a cause of uncertainty. It has to be made, so far as the parents are concerned, almost entirely from records. In dealing with case notes made forty or fifty or, it might be, eighty or ninety years ago, I found that besides obsolete terms, internal contradictions, very brief histories, and other such deficiencies, I was frequently compelled to ask myself whether drugs (the psychiatrists were fond of sulphonal, for example), malnutrition, and medical and nursing attitudes might not have been responsible for the development of chronic illness, or of "organic" features, leading to an incorrect retrospective diagnosis. The social, psychological and material environment of some mental hospitals could, and still does, produce artefacts—violent outbursts, withdrawal and preoccupation with fantasies, eccentric habits, despair, distrust, paranoid beliefs, decay of self-respect—symptoms which might not have occurred if the patient had been discharged from the hospital at an earlier stage, and which impose, as it were, a chronic course on what could perhaps have been an acute, transient illness, so that the appearance of schizophrenia is added to an initially affective disorder. All this is in addition to the intrinsic troubles of psychiatric diagnosis, so difficult to resolve when dealing with the psychoses of middle age; involuntional psychoses, with paraphrenic features developing in the setting of an agitated depression or an Angstpsychose, are one example of this, and the paranoid schizophrenic illness that ensues upon an acute alcoholic hallucinosis is another.

Finally, there are the difficulties of analysing the material, especially when it is no larger than the series under discussion. Until the clinical entities with which we work are more securely based on objective, unequivocal somatic and psychological observations, we can neither safely add the findings of one series to that of another, nor assume biological identity of syndrome or disease because of clinical similarity. It is sometimes said that genetic studies may serve to define psychiatric diseases and subgroups more effectively than the clinician has so far been able to: this may well be, but it seems unlikely that studies of "conjugal psychoses" will be the chosen instrument. Much thorough-going effort, technical resources, experience in clinical-genetic research, ingenious analysis and reasoning, and critical

judgment has been expended on the inquiries by *Schulz* and *Elsaesser* to which I have repeatedly referred: but the yield in unambiguous conclusions is meagre.

The work would be easier and more complete in a country which had a central register so organized that it permitted bona fide investigators to ascertain the lifelong record of psychiatric illness for everybody who had been seen at a hospital, clinic or outpatient department of any kind. But even if this improbably complete register were to exist, the other sources of error and misjudgment would still make it doubtful whether a large scale inquiry into the offspring of two psychotic parents can justify itself by its results. It could not, I believe, until we have a surer taxonomy of mental disease.

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A SECOND INVESTIGATION INTO THE CHILDREN OF COUSINS ADMITTED TO PSYCHIATRIC HOSPITALS

By E. SLATER and W. L. B. NIXON

An investigation is described into patients admitted to psychiatric hospitals who were ascertained to be the children of cousins. It represents a continuation of earlier work by *Shields* and *Slater*. Propositi so ascertained were matched with control cases. Marriages of first cousins, or even closer relationships, were ascertained in 167 cases, remoter relationships in 75. Unions between double first cousins, between uncle and niece and uncle and half-niece, and between father and daughter were found. The commonest

type of consanguinity between first cousins was the marriage of the children of two sisters. Minority religious groups were over-represented and Roman Catholics were under-represented in the *propositi*. The *propositi* were significantly less frequently married, and if married had fewer children, than the controls. Classification of diagnoses in *propositi* and controls showed a significant excess of schizophrenia in the former. The significance of the difference was maintained if hospital diagnoses, rather than our personal diagnoses, were used. In the schizophrenic *propositi* there were 33 males and 33 females, in the control schizophrenics there were 16 males and 29 females. The findings are thought to support the hypothesis that autosomal recessive genes play some part in the aetiology of schizophrenia. No clinical differences were found between schizophrenic *propositi* and schizophrenic controls. The data may be used to provide rough estimates of the frequency of cousin marriage in the parents of schizophrenics, of the frequency of the hypothetical recessive gene, and of the fraction of the totality of schizophrenia which may be accounted for on the recessive hypothesis.

Discussion

Ø. Ødegård (Oslo): Dr. Slater has found an excess of schizophrenic cases among patients with consanguineous parents, and he concludes rightly that this supports the hypothesis of recessive inheritance. But this naturally depends on whether his consanguineous group and his controls are comparable samples of the proportion of the London area with respect to the incidence of schizophrenia. This is important, because it is known that this incidence varies as much as 100%, or more from one social group to another. The information given about the consanguineous group does not allow definite conclusions, but it struck me that certain minority groups were markedly over-represented. Could it be possible that in these groups (immigrants, jews, non-conformists) there is a relative excess of schizophrenia? In view of previous epidemiological findings this is not unlikely. After all schizophrenia might be called a "non-conformist disease".

E. Essen-Möller (Lund): The major argument against recessivity in schizophrenia is that the incidence in children of schizophrenics is rather high as compared with the incidence in siblings. Would it be possible, then, to show that this proportion between schizophrenic siblings and children (of schizophrenic probands) is different in cases where the probands descend from consanguineous parents and so are liable to belong to a recessive type of schizophrenia?

H. Slatis (Lemont, Illinois): It would appear, as noted in papers previously presented at these meetings, that the individuals in a consanguineous marriage may have had difficulties in choosing a mate. Thus with a mental condition that may be dominant, we may have a slight manifestation in an individual, resulting in an increased chance of the person contracting a consanguineous marriage. Expression of this poorly penetrant dominant in children of such consanguineous marriage would then appear to be a case of recessive inheritance where dominant inheritance is actually the case.

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A STUDY OF PSYCHOTIC PATIENTS OF CONSANGUINEOUS PARENTAGE

By Ø. ØDEGÅRD and H. HERLOFSEN

A preliminary report of our investigation was given in the *Tage Kemp* anniversary number, and here I shall only give some of the headlines and must omit the tables.

In Norway, admission to mental hospitals demands a medical certificate, and one of the questions to be answered is: Are the parents of the patient related to each other? Generally the doctor is the local public health officer who has been resident in the district for many years and therefore knows the people well. In addition, he is expected to contact the patient's next of kin, and most people in Norway have a fairly complete knowledge of their grand-parents. From four hospitals in eastern Norway and one in Bergen (western Norway) we therefore examined the admission-forms and case-histories of 11,145 first admissions from the period 1926-1955, and the result was: 119 cases where the parents of the patient were first cousins (59 men and 60 women). We have not included the patients whose parents were second cousins. There should have been nearly three times as many of these compared with the first group (*Wulz*), and as we only found a fraction the material would be incomplete. As to the completeness of the first group we found that the afore mentioned question was answered in about 75%—as a check up we therefore sent personal letters to relatives of 331 patients admitted in recent years to one of the eastern hospitals. Answers were received from 82%, but no new information as regards consanguinity was obtained. There is probably no reason to believe that the statement about consanguinity on the forms should be more complete or more often correct in any special of the functional psychoses. But in general paresis and other organic psychoses the question is perhaps more often

neglected as the taint here probably does not interest the doctor. Our 11 organic psychoses are therefore excluded. It might be argued that readmission could be a source of additional information about consanguinity, and this was actually the case for one of our probands. Generally, the question was not answered in these instances so we do not think that the periodic psychoses are overrepresented on this account.

The rate of consanguinity in different parts of Norway is not known, but can be estimated to be around 2 % in rural districts and 1 % or less in the cities. In our material the consanguinity rate among the first admissions is very nearly the same in the four eastern hospitals, and here it is also the same for cities as for urban districts—0.90 %. The western hospital receives patients from Bergen (with 100,000 inhabitants, the second largest city in Norway), as well as from the rural county a distance to the north (Sogn og Fjordane); the rates are here 0.90 % and 3.4 % respectively. The striking difference between this western county and the eastern districts most likely reflects a corresponding difference in the consanguinity rate of the general population, as small isolates are much more common in the western fiord and mountain district than in the agricultural east.

It is generally assumed that the consanguinity-rate is decreasing because of breaking up of isolates. The rates from the two halves of the period of investigation are 1.42 as against 0.89, but this great decrease is probably partly due to the increasing number of admissions by psychiatric specialists who tend to take the admission-forms less seriously.

The consanguinity-rate we have found corresponds approximately to the rate in the Norwegian population. And even with a clean-cut recessive disease one would not expect the rates to be much greater when the disease is as common as the two in question, schizophrenia and manic depressive insanity. In our material these two groups have a consanguineous percentage of 1.1 and 2.6, respectively. This was rather surprising, in the light of the findings of *T. Larsson* and *T. Sjögren*, two years ago, in a large Swedish rural population, 3.7 and 2.4, while in the general population it was 2.5.

Now we have compared the consanguineous group (excluding the 11 cases of organic psychoses for reasons already mentioned) with a control material consisting of 202 patients which have, in connection with another proband-investigation, been selected at random among the first admissions to two of the four eastern hospitals. Both groups date from approximately the same period and both have been treated exactly alike: Complete abstracts from the case-histories were prepared by trained medical assistants or by us, and by a lot of travelling we have tried to contact personally at least two members of each family. In addition, letters and inquiries were sent

to nearly all sorts of public institutions and this part of the work is still not finished. As the patients came from five hospitals during a period of 30 years and psychiatric diagnoses being what it is one of us (*Ødegård*) has reclassified and coded each of the probands.

The comparison then reveals a series of significant differences. In the consanguineous group there is more manic depressive insanity and less schizophrenia, and within the heterogenous group of reactive psychoses (psychogenic, with constitutional psychopathic inferiority) the depressive forms predominate over the paranoid. We find further in the consanguineous group that of the syndromes there is an excess of depression and excitement, of the symptoms disturbance of mood and affectivity tends to take the form of depression or elation rather than irritability and temper tantrums, and the delusions tend to be self-deprecatory or grandiose. Acute onset and a periodic course with good or fair remissions predominate.

We also compared the consanguineous group, now with the original diagnoses, with the first admissions to the same five hospitals counting every fifth year, and as before, we found that manic depressive insanity is more than twice as frequent as in the control group but the incidence of schizophrenia is here approximately the same in both groups.

These significant differences seem to indicate that recessive inheritance is relatively more important for the affective psychoses than for the paranoid and deteriorating types. But what do we know of what is lying behind the figures?

In between one third and one half of the families there were more cases of cousin-marriages, so that in some families there is a rather marked tendency to in-breeding. In three instances we were told it was in order to keep the property in the family, but generally the relatives explained it on account of the isolate.

It is conceivable that a person with a predisposition towards affective psychoses will marry within his own circle, and an opposite trend may be at work in individuals of schizoid constitution. We know that the schizophrenics have a definitely decreased marriage-rate (as *Ødegård* has shown), and this might also be the case for his nearest relatives. This would make it unlikely for two such persons to marry. This is thus one possible explanation for our low rate for schizophrenia. A further possibility is that in a small community a serious and well-known hereditary taint may lead to inbreeding, because members of such families may feel thrown upon themselves, or perhaps are actually feared as potential partners. This seems to be the case for one of our probands, a man with Huntington's chorea, living in a small community where everybody knew about the disease and

most feared it. In his family the tendency to inbreeding was very strong. It is natural that dominant inheritance should be more easily noticed and recognized than recessive. On the other hand, affective psychoses are relatively benign, and it does not seem to be common experience that members of manic-depressive families refrain from marriage or are in any way avoided because of the taint, although the amount of psychoses among their relatives is much greater—nearly twice as much—as that among the relatives of the schizophrenics. Because of the higher incidence rate of consanguineous marriage in rural districts we have a difference between our two groups as to the origin of the probands that may well influence our figures on account of the excess of schizophrenia in the cities but cannot fully explain the difference.

The crude incidence-rate for psychoses among the relatives (sibs, parents, uncle and aunts) seems to give the usual values. But when we compare the relatives' diagnoses among the schizophrenic and the manic-depressive probands the schizophrenics seem to have nearly the same number of manic-depressive relatives as of schizophrenic relatives. This finding is not finally established yet, but I mention it since it was rather surprising.

The nature of relationship is verified among 108 probands (four were children of double-first cousins, two schizophrenics and two manic-depressives), and divided for relationship we find

mm	mf	fm	ff
28	25	28	31

A prejudice against marrying a person with the same surname does probably not hold for Norway, where the surname, by the way, is often taken from the name of the farm.

In case of partial sex-linkage (and no crossing over) a male is known to derive his heredity from his father's father, and a female from her father's mother. We can then make two tables.

	Schiz.		Non Schiz.	
Males	16	13	12	12
Females	6	11	19	23

$\chi^2 = 0.66$, $0.10 < P < 0.20$. The figures indicate a difference between these two groups, but Chi square shows no significance, possibly because the figures are too small, and the schizophrenic disease is too prevalent. I regret that these results are rather meagre, but further proband investigation may be able to throw more light upon these problems.

Discussion

Ø. Ødegård (Oslo): I should like to point out that our findings are directly opposite to those of Slater, and our conclusion would be that schizophrenia is "less recessive" or "more dominant" than manic-depressive psychosis.

Now the relative preponderance of affective psychosis which we have found among the offspring of first-cousin marriages may result from these matings being selective, and Dr. Herlofsen pointed out some of the possibilities. I should like to add that in these parts of Norway consanguineous marriages may be more common in the classes where there is some property which should be kept within the family. And my own studies (to be published) show that there is an excess of schizophrenia within *underprivileged occupations*, while manic-depression is more evenly distributed.

There is also the possibility that manic-depression is more genetically determined, while in the vast group of schizophrenias an admixture of non-inheritable cases is more likely.

These contradictory findings call for a detailed analysis of possible differences between consanguineous mates and the general population. Besides an enlargement of the material is desirable.

Mitsuda, H.: Acta genet. 7, 371-377, 1957

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KLINISCH-ERBBIOLOGISCHE UNTERSUCHUNG DER ENDOGENEN PSYCHOSEN

Von H. MITSUDA

Verschiedene Umstände wirken hemmend auf den Fortschritt der genetischen Forschungen im Bereich der endogenen Psychosen. Eines der größten Hindernisse dürfte vielleicht darin bestehen, daß man sich noch immer nicht darüber klar ist, ob von den bekannten klinischen Formenkreisen jeder für sich als biologische Einheit anzusehen ist oder nicht. Die Frage der Heterogenie scheint heute, was die endogenen Psychosen anbelangt, das Stiefkind der erbbiologischen Forschung zu sein. Es erübrigt sich zu sagen, daß man trotzdem um diese Frage nicht herum kann, um so weniger, als im Bereich der allgemeinen menschlichen Erbpathologie immer mehr Beispiele für die Heterogenie bei phänotypisch anscheinend einheitlichen Erb leiden bekannt geworden sind.

Ich selbst habe mich nun schon seit langem bemüht, die endogenen Psychosen vom klinisch-genetischen Gesichtspunkte aus einzuteilen, indem ich zuerst die großen Erbkreise der endogenen Psychosen klinisch in verschiedene Untergruppen einteilte und dann für diese einzelnen Untergruppen die intrafamiliäre Variabilität untersuchte. Abb. 1 zeigt eine grob

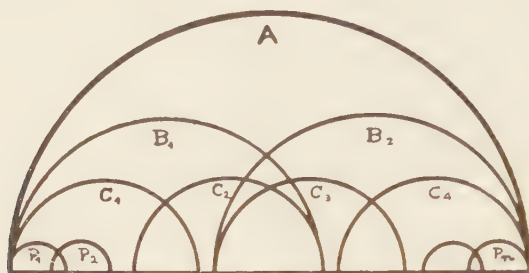


Abb. 1. Schematische Darstellung der klinisch-erbbiologischen Einteilung der endogenen Psychosen.

schematische Darstellung einer solchen klinisch-erbbiologischen Einteilung. Der Grundgedanke dieses Versuchs ist eine Analogie zu dem bekannten Johannsen'schen Versuch einer Selektion der reinen Linien. Obwohl man zur Zeit noch nicht imstande ist, im Bereich der endogenen Psychosen eine Erbeinheit, wiederum im Sinne einer Analogie zur Selektion der reinen Linien, herauszufinden, kann man doch versuchen, aus der Gruppe A die B- und C-Reihen von Untergruppen auszulesen, und zugleich mit besonderer Berücksichtigung der Überschneidung der phänotypischen Manifestationsbreite eine genetische Beziehung zwischen den einzelnen Untergruppen festzustellen. Tab. 1 zeigt die intrafamiliäre Variabilität der großen endogenen Psychosen. Ich möchte hier kurz einige Bemerkungen vorausschicken. In dieser Arbeit habe ich Gewicht darauf gelegt, den Prozentsatz der Sippen mit Sekundärfällen der gleichen Psychosen wie beim Probanden einerseits, und den Prozentsatz der Sippen mit Sekundärfällen heterotypischer Psychosen andererseits festzustellen. Die angegebenen Prozentzahlen beziehen sich nicht auf die Häufigkeit der Sekundärfälle, sondern auf die Anzahl der Sippen mit mindestens einem Sekundärfall der betreffenden Psychosengruppe.

Wie aus der Tabelle ersichtlich ist, zeigen die drei Erbkreise, unter Ausschluß der Degenerationspsychose *, in ihren Familienbildern wohl eine

* Die Degenerationspsychose habe ich etwas enger, als es bei der Kleistschen Schule üblich ist, gefaßt.

Tabelle 1. Intrafamiliäre Variabilität innerhalb der einzelnen klinischen Gruppen bei endogenen Psychosen

Proband	Anzahl	Familienpsychosen				
		Schizo- phrenie	MDI	Epi- lepsie	Alters- psychose	Unklare Psychose
		%	%	%	%	%
Schizophrenie	331	52.3	11.5	10.3	8.2	12.1
MDI	217	22.1	47.5	13.8	9.7	18.8
Epilepsie	124	20.1	4.8	19.4	3.2	8.9
Degenerationspsychose	55	50.9	20.0	30.9	5.5	16.4

Tendenz zur Homotypie, sie haben aber doch zugleich ihre phänotypischen Manifestationen in einer verhältnismäßig großen Breite gemeinsam.

Tab. 2 zeigt die intrafamiliäre Variabilität der einzelnen Typen bei Schizophrenie. Dabei habe ich solche Fälle als typische Form, d. h. als Kerngruppe zusammengefaßt, bei denen Autismus, Verödung der Affektivität und des Willenslebens, kurz, mehr oder weniger deutlich die regressive Tendenz festzustellen war. Dagegen umfaßte die atypische Form, nämlich die Randgruppe, solche Fälle, die meistens episodisch oder periodisch verworrene, stuporöse oder oneiroide Zustände zusammen mit verschiedenen akzessorischen Symptomen aufwiesen. In die intermediäre Form wurden schließlich alle die Fälle vorläufig aufgenommen, welche sich sonst in die beiden obigen Untergruppen nicht leicht einordnen ließen. Darunter fand sich aber eine Reihe von Fällen, welche mit einem atypischen Krankheitsbilde begannen, um dann unmittelbar oder erst nach dem

Tabelle 2. Intrafamiliäre Variabilität bei Schizophrenie

Proband (Typus der Schizophrenie)	Anzahl	Familienpsychosen				
		Schizophrenie			MDI	Epi- lepsie
		chro- nisch %	remittie- rend %	akut- tödlich %		
Typisch	182	39.6	7.1	0	2.8	4.4
Atypisch	102	13.7	49.0	9.8	23.5	21.6
Intermediär	32	28.1	46.9	3.1	25.0	12.5
Paraphrenisch	15	66.7	6.7	0	6.7	0

periodischen Ablauf in einen mehr oder weniger deutlichen Defektzustand zu geraten.

Wie aus der Tabelle ersichtlich ist, besteht eine deutliche Erhöhung der Prozentzahl der mit chronischer Schizophrenie belasteten Sippen bei der typischen Form gegenüber der atypischen. Dagegen zeigt die atypische Form eine hohe Prozentzahl von mit remittierender Schizophrenie belasteten Sippen und zugleich eine starke Tendenz zu heterophäner Manifestierung. Wie Sie sehen, ist unter den Familienpsychosen die prozentuale Verteilung in den Rubriken «Manisch-depressives Irresein» und «Epilepsie» bei atypischen Probanden bedeutend höher als bei typischen.

Tabelle 3. Intrafamiliäre Variabilität bei manisch-depressivem Irresein

Proband (Typus d. MDI)	Anzahl	Familienpsychosen				
		Schizophrenie			MDI %	Epilepsie %
		chronisch %	remittierend %	akut-tödlich %		
Rein	47	8.5	2.1	0	68.1	4.3
Agitiert-depressiv . . .	46	8.6	19.5	6.5	47.8	19.6
Verworren-manisch . .	53	3.8	20.8	1.9	34.0	26.4
Involutionsmelancholie .	35	8.6	17.1	0	54.3	5.7

Tab. 3 zeigt die intrafamiliäre Variabilität des manisch-depressiven Irreseins. Ich möchte nur darauf hinweisen, daß auch hier bei agitiert-er Depression oder verworrener Manie, also bei der atypischen Form, die prozentuale Verteilung in den heterotypischen Rubriken unter den Familienpsychosen deutlich erhöht ist.

In Tab. 4 wurde die intrafamiliäre Variabilität bei Epilepsie und Degenerationspsychose zusammengestellt. Im epileptischen Kreis haben wir die Fälle der typischen Kerngruppe, welche ausschließlich Anfälle im Sinne eines «grand mal» mit oder ohne «petit mal» zeigten, von denen der atypischen Randgruppe abgegrenzt, welche daneben noch psychische Äquivalente bzw. psychomotorische Symptome aufwiesen. In letztere Gruppe wurden außerdem die Fälle mit positivem *Erb'schem* Phänomen, nämlich die sogenannte tetanoide Epilepsie eingeordnet. Wie aus der Tabelle ersichtlich ist, besteht auch hier bei den Psychosen in den Familien der atypischen Probanden eine Erhöhung der prozentualen Verteilung in den heterotypischen Rubriken gegenüber den typischen.

Tabelle 4. Intrafamiliäre Variabilität bei Epilepsie und Degenerationspsychose

Proband		Anzahl	Familienpsychosen				
			Schizophrenie			MDI	Epi- leptie
			chro- nisch %	remittie- rend %	akut- tödlich %		
Epil.	typisch	83	2.4	6.0	1.2	3.6	18.1
	atypisch . . .	41	17.1	31.7	0	7.3	22.0
Degenerationspsychose .		55	0	41.8	3.6	20.0	30.9

Auf die Degenerationspsychosen möchte ich hier wegen der Kürze der Zeit nicht eingehen.

Wenn wir nun die bisherigen Ergebnisse betrachten, so kann man annehmen, daß innerhalb der endogenen Psychosen, was die Erbanlage betrifft, die atypischen Untergruppen gegenüber den typischen in ihren phänotypischen Manifestationen erheblich größeren Schwankungen unterworfen sind und sich gelegentlich überschneiden können.

Tabelle 5. Intrafamiliäre Variabilität innerhalb der einzelnen klinischen Typen bei endogenen Psychosen *

Proband		Familienpsychose							
		Schizophrenie				MDI		Epil.	
		typisch	intermed.	atypisch	paraphren.	typisch	atypisch involutiv	typisch	atypisch Degenerations- psychose
Schizophrenie	typisch	56	3						
	intermed.	2	4	5		1			2
	atypisch		3	22	2	1	5	1	2
	paraphren.			1	3				4
MDI	typisch					6		1	
	atypisch		2	5		1	9	2	1
	involutiv					2	3	2	
Epil.	typisch			1				3	
	atypisch			2				2	
Degenerationspsychose									2

* hier nur Fälle mit persönlicher Untersuchung der Familienpsychosen

Um dieses Ergebnis noch weiter zu sichern, habe ich ferner aus dem gesamten Material solche Sippen ausgewählt, in denen die Sekundärfälle von mir persönlich untersucht worden sind. Ich habe von neuem ihre intrafamiliäre Variabilität eingehend nachgeprüft. Wie Tab. 5 zeigt, besteht ein wesentlicher Unterschied zwischen den Familienbildern der typischen Untergruppen und denjenigen der atypischen, vor allem bei der Schizophrenie. Die typische Kerngruppe der Schizophrenie von insgesamt

Tabelle 6. Schizophrene Zwillinge (Mitsuda, Okamoto, Hayashi)

Nr.		Alter	Ge- schlecht	Erkran- kungs- alter	Krank- heits- form	Verlauf	Defekt	Beurtei- lung der Ähnlich- keit
1	EZ	17	A ♂	± 12	typisch		++	=
			B ♂	± 10	typisch		##	
2	EZ	29	A ♀	22	typisch		++	=
			B ♀	22	typisch		++	
3	EZ	25	A ♀	24	intermed.		++	=
			B ♀	22	intermed.		##	
4	EZ	25	A ♂	19	typisch		++	=
			B ♂	24	typisch		##	
5	EZ	29	A ♀	19	atypisch		±	I
			B ♀	19	intermed.		##	
6	EZ	29	A ♀	27	intermed. ?		##	I
			B ♀	24	atypisch		±	
7	EZ	23	A ♀		Schizoid			∞
			B ♀	21	typisch		##	
8	EZ	29	A ♂	18	typisch		##	∞
			B ♂		Schizoid			
9	EZ	33	A ♀		Schizoid			∞
			B ♀	32	typisch		±	
10	EZ	20	A ♂	19	typisch		+	∞
			B ♂		Schizoid			
11	EZ	28	A ♂		unauffällig			×
			B ♂	27	atypisch		±	
12	EZ	18	A ♀		unauffällig			×
			B ♀	17	Degenerat.*		—	
13	ZZ	25	A ♀	25	Degenerat.*			×
			B ♀		unauffällig		—	

* Degenerationspsychose.

59 Fällen weist mit Ausnahme von drei Fällen eine starke Tendenz zur Homotypie auf, während in den Sippen der atypischen Randgruppe sowohl manisch-depressive als auch epileptische Kranke zuweilen vorkommen. Dasselbe gilt auch in annähernd entsprechender Weise für den Erbkreis des manisch-depressiven Irreseins.

Tab. 6 zeigt die Ergebnisse unserer eigenen Untersuchung bei schizophrenen Zwillingen. Wenn auch die Anzahl unserer Fälle keineswegs genügt, einen bindenden Schluß daraus zu ziehen, so soll doch erwähnt werden, daß in unserem Material kein einziges Zwillingspaar beobachtet wurde, bei dem typische und atypische Krankheitsbilder der Schizophrenie zusammentrafen.

Ich komme zum Schluß. Es läßt sich also zusammenfassend folgendes sagen: Die drei großen endogenen Psychosen, vor allem die Schizophrenie, sind meiner Ansicht nach, erbblologisch betrachtet, in sich eher heterogen als homogen. Wenn man zum Beispiel die großen Erbkreise jeweils in eine Kern- und Randgruppe einteilt, muß es auffallen, daß zwischen den Randgruppen gewisse phänotypische und genetische Übereinstimmungen bestehen, während die Kerngruppen weitgehend selbständig sind.

Philipsen-Prahm, H.: Acta genet. 7, 377-380, 1957

University Institute of Human Genetics, Copenhagen,
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ON MENTAL ILLNESS IN DANISH TWINS

(Preliminary Report)

By H. PHILIPSEN-PRAHM

The purpose of this investigation, which started in April 1955, is to elucidate problems concerning the significance of heredity and environment, or more correctly, their rôle in the development of psychosis, neurosis, deviations of character (psychopathies and character neurosis) and mental defect, the basic question being why mental illness is only manifested by some and not other cases.

The principle, as far as possible, has been to use a representative, non-evaluated series of twins born during a well-defined period, within a geographical area large enough to give a reasonably adequate number of index cases, and yet so limited that it is possible to visit personally the different twins and their families.

The initial material is at present being collected under the direction of Dr. *Harvald* and Dr. *Hauge* (Danish Medical Bulletin, August 1956), and their material constitutes the basis for the psychiatric investigation.

All twins born in the period 1870–1910 are being listed from the registers of newborn in Denmark. The total number is estimated to be 30–35,000 pairs of twins. Their present residence or death is then ascertained by examining the Census Returns, the National Registrations and the Registers of Deaths.

Almost 10,000 pairs of twins (9360) have been found to date in the Registers of Births. Of these, almost 3000 pairs have been excluded from the investigation on account of the death of one or both twins prior to the age of five, and further 2000 pairs because it has been impossible to trace them.

Of the remainder, totalling 4460 pairs of twins, 1900 pairs have already been questioned concerning their illnesses.

Apart from these, we hope to be able to find a further 1000 pairs or more so that we can obtain data on 3000 pairs out of the 10,000 pairs born.

The present material so far only comprises the area east of Lillebælt, so that Jutland is not yet included. As the investigation proceeds, we expect to find 6000 pairs east of Lillebælt, the total available material for Denmark thus increasing to 9–10,000 pairs.

In order to obtain an ideal non-evaluated series of twins with mental illness I ought to visit all traced living twins in order to appraise them psychiatrically—but this seems to be an insurmountable task.

I have considered whether I should limit the psychiatric investigation to those twins who have been referred to psychiatric departments or hospitals but in order to find all of them, it would be necessary to compare the patient-registers of all these hospitals with the traced twin material. But as such patient registers do not exist for the distant past, this procedure has been dismissed as impracticable.

The index cases for the psychiatric research comprise the following like-sexed twin pairs: (a) cases where the twins or their nearest relatives stated in the questionnaire, that the twins had been mentally ill, (b) cases where mental illness is apparent from the case-histories of the hospitals mentioned by the twins in the returned questionnaires, (c) cases where the questionnaires were not returned, and where the twins concerned have therefore been visited and have then given information about mental illness or have otherwise proved to have suffered from a mental disease.

Of the 1900 twins traced until May 1956, it was *in this way found 80 like-sexed pairs*, which had manifested mental illness. Of these 25 pairs were monozygotic (9 male and 16 female) and 55 dizygotic (19 male and 36 female). Out of these 16 DZ and 28 DZ pairs are still alive.

68 pairs of which 20 DZ and 48 MZ have been in-patients at psychiatric hospitals or wards, neurological departments, medical departments or general hospitals, and institutions for mental defectives. The remaining 12 pairs consist of some, who had not returned the questionnaire but were visited and considered to be mentally ill. Out of these, one twinpair was found to be included in the register of the psychiatrist attached to the police. The others are twins whose Death Certificate recorded suicide, but where neither the index twin or his her partner has been an in-patient at any of the above institutions.

The distribution of the different unrevised diagnoses is the following: 6 mental defectives, 14 schizophrenic, 12 manic-depressive psychosis, 11 depressive neuroses, 25 other diagnoses i.e. other types of neuroses, psychopathy and organic psychoses, 12 suicides.

Meanwhile the different proportions cannot be regarded as representative until the complete material, is available, and so it is not yet possible to draw any conclusions.

The method of treating the psychiatric material: Detailed abstracts were first made of the hospital case-histories. I then visited the surviving twins and interviewed each person at least once at their homes. Special stress was laid on information concerning childhood, but unfortunately it has been almost impossible to obtain vital information regarding emotional contact and care during the first years of life. It was, however, possible to procure some data relating to kindergarten and school, as well as with regard to the atmosphere in the home during these periods.

Heredity tainting is being investigated, and it is proposed to trace the pedigrees.

I have further attempted to obtain as full a record as possible of somatic diseases, as well as behaviour, pattern of reaction, temperament and character in childhood and in later life. In addition to this, a record is made of the lives, work, marriages, interpersonal relationships, and the beginning, development and course of the mental illness, of the twins.

Neither intelligence tests nor Rorschach test were employed on these twins.

The *diagnosis of ovularity* is based on blood grouping (at least 8 systems), colour of iris, type of hair, shape of ears, early photographs and

information regarding similarity, mistaken identity and colour of hair in childhood.

Out of 10 000 pairs of twins, 1900 have been traced, 80 of whom have been found to be psychiatric cases. We expect to be able to trace 3000 pairs, which will possibly provide me with 130 pairs suffering from psychiatric diseases (40 MZ and 90 DZ). If the collection be continued until we have found all twins in Denmark, we will possibly trace 9-10000, thus obtaining a total of about 400 pairs of psychiatric cases (125 MZ and 275 DZ).

The intention is to ascertain to what extent there is concordance or discordance on these points, mentioned above. I am especially interested in discovering whether it is possible to demonstrate any negative or positive correlation between childhood surroundings and the manifestation of mental illness and deviations of character.

This problem would probably be best elucidated by research on twins reared apart. However where twins have *not* been separated in early childhood there is a possibility of detecting the result of different acceptance and handling of the twin-pair members, as in such unseparated pairs we often find a very uniform external environment, whereas the emotional surroundings of one twin may appear to be different from those of the other even in the same home.

Denmark seems to provide especially favourable conditions for this type of investigation. Firstly, the registration of births and of residence is as perfect as possible, and the country extends over such a comparatively small area that both tracing and visiting is feasible.

Discussion

E. Essen-Möller (Lund): Wants to report a similar non-selective register of twins is in existence at the Psychiatric Clinic, University of Lund, Sweden. This register comprises all the twins ever born within the province of Scania from 1880 to 1945.

ON THE IMPORTANCE OF HEREDITY IN MENTAL DEFICIENCY

Reed, S. C., and E. W. Reed: *Acta genet.* 7, 381-382, 1957

Dight Institute for Human Genetics, University of Minnesota, Minneapolis, Minnesota,
U.S.A.

THE RELATIVES OF THE MENTALLY RETARDED

By S. C. REED and E. W. REED

Pedigree study is still a fundamental method for obtaining information about the interaction of heredity and environment in the etiology of any trait. We now have 150 completed pedigrees of the relatives of *propositi* who were mentally retarded. The individual family groups vary in size up to the largest one which encompasses 761 persons. The pedigrees extend for from five to seven generations. The families were studied first between 1911 and 1918 by *Deavitt* and *Curial* and the project reopened by the authors in 1949.

Intelligence tests and data on occupations, education and social adaptation of the *propositi* and some of their relatives were obtained by the first workers. Comparable material for the later generations was collected by the authors.

It is well known that the I. Q. value and social data for one person may give little information as to the relative contributions of heredity and environment to the development of intelligence. It was found that the picture shown by the I. Q. values and social data for the whole family group when compared with other groups was most illuminating.

Replacement rates of the more distant relatives of the *propositi* were higher than those of the closer relatives.

The 150 patients and 79 retarded relatives of the third and fourth generations, who were also institutionalized, produced only 84 children, an average of 0.37 children per person. The average I. Q. of the retarded institutionalized persons was 56.2 and for their children it was 80.8, a gain of 24.6 I. Q. points for the children, compared with the retarded parents.

The brothers and sisters of the patients produced only 1.2 children each, on the average, with an average I. Q. of 101.2. These nephews and nieces

have not completed their families yet but have already produced an average of 1.6 children each, with an average I. Q. of 105.8. The chronological contemporaries of the *propositi*, their first cousins, produced 1.9 children with an average I. Q. of 103.5. The latter are practically at the replacement level of approximately 2.2 children.

Thus we see that the factors responsible for mental retardation are not self sustaining but tend to decrease in our families. Presumably the mentally retarded are replaced in the general population by new deleterious mutations and new environmental changes for the worse, as is the usual case for physical abnormalities.

Larson, C. A.: *Acta genet.* 7, 382-385, 1957

Institute of Genetics, University of Lund, Sweden

SOME ASPECTS OF KIN MATINGS WITH MENTALLY DEFECTIVE OFFPSRING

By C. A. LARSON

This report gives data on kin matings between parents of mental defectives, born and institutionalized within the South Swedish region of Götaland (population 3.4 millions). Differences between rural and urban districts with respect to the incidence of such matings are discussed.

Of 4,825 inmates of institutions 2,854 (59.2 per cent) were born in rural districts. In 90 (3.2 per cent) instances of rural births the parents were found to be related. Such was the case in 22 (1.1 per cent) instances of urban birth.

The number of matings between known partners, giving rise to either only rural or only urban probands, was 4,206. Of these matings, 2,454 (58.3 per cent) were rural. Of the rural matings 84 (3.4 per cent) were between related partners, while 20 of 1,752 (1.1 per cent) of matings between urban residents were of related persons. The difference between rural and urban births with respect to parental consanguinity was significant with *P* less than 0.001 ($X^2 = 22.062$, 1 D. F.).

The offspring from kin matings included 14 inmates from an equal number of incestuous unions, 13 of their mothers were rural residents. In 9 cases of incest at least one partner was mentally subnormal or defective.

From 28 matings between persons more remotely related than first cousins came 29 defectives, 26 of them from 25 rural matings. The relationship in these 28 instances was, as in all other cases of relationship specified in this report, secured through objective genealogic methods.

Of 69 inmates originating from first cousin matings, 51 (74 per cent) were born in rural communities. They constituted 1.8 per cent of the 2,854 inmates from rural birth communities, as compared with 0.9 per cent (18: 1,971) of urban probands originating from first cousin matings.

In 11 of 62 matings between first cousins, one or both partners were mentally subnormal or defective, the same proportion was observed in matings between unrelated persons. Exclusion of such matings, and also of matings secured only through index cases of brain injury sequels, left for comparison 50 first cousin matings and 3,019 matings between unrelated partners. Thirty-seven (74.0 per cent) of the former, and 1,767 (58.5 per cent) of the latter were between rural residents.

Thus kin matings with mentally defective offspring were relatively more common in rural than in urban districts. This trend was observed for all classes of consanguineous matings. The preponderance of incest in rural districts was probably symptomatic of the higher incidence of mentally defective or subnormal persons in rural areas (*Lewis* [1929]; *Penrose* [1938, 1949]). The difference between rural and urban births within the other classes of consanguineous unions corresponds to a higher incidence of kin matings among rural residents.

Bergsten [1951] divided South Sweden into a broad western belt with a relatively high percentage of residents born within their residential community, and an eastern region with a more mobile population. An intermediary mobility was represented by a zone between those regions, and also by some districts in southernmost Sweden. Regions with a low migration trend were characterized by a relatively high married fertility rate within the agricultural population, compared with a low fertility in regions with a high frequency of migration.

Within that western region *Larsson* and *Sjögren* [1954] studied a rural district, chosen partly because the annual influx of new residents was the lowest for any district in Sweden. For parents of children born in the district during the period 1861 to 1920, they observed a first cousin frequency of 2.6 ± 0.6 for the native population, and 2.3 ± 0.6 for the resident population. In the southern and most densely populated county

of Sweden I obtained through random selection among 212 rural communities a parish which happened to be situated in a district characterized by an intermediate population mobility. The observation that 1.9 per cent of the marriages contracted in this community (1901-1952) were between first cousins, gave rise to the question whether the incidence rate of first cousin marriages observed by *Larsson* and *Sjögren* could be valid, at least until recently, for wide rural regions. In another randomly selected rural community that bordered on the first one, an examination that has not yet been concluded, revealed that 2 of 310 marriages were contracted by first cousins. In the two communities a total of 661 marriages were examined sufficiently to show whether the partners were first cousins. This was the case in 12 (1.8 per cent). Dividing 225 marriages with incompletely known ancestries of partners into 2 halves, considering 113 examined and 112 not examined, results in 774 unions between known partners, after addition to the completely examined marriages. Then 12 of 774 couples were first cousins (1.6 per cent). A suitably selected parish in a South Swedish city with 200,000 inhabitants was covered by this study. So far 565 marriages, contracted in 1950 to 1952, have been examined, 1 of them was between first cousins.

So far the incidence of first cousin matings between parents of institutionalized mental defectives has not been observed to be essentially higher than the first cousin marriage frequency in some rural districts. About 18 per cent of institutional inmates originating from first cousin matings seemed to have the mental endowment of their parents. In this respect those inmates agreed with probands of unrelated parentage. Thus the observation of mental deficiency in a person whose parents are first cousins allows no immediate conclusion as to the mode of inheritance.

These observations cannot obscure the theoretically and empirically well founded tenet that kin matings bring to the fore concealed detrimental inheritance. Normal population groups and the series of rural defectives in the present study exhibit no such clear cut differences with respect to kin matings as observed by *Penrose* [1938, 1949]. In the normal populations being investigated the ascertainment of first cousin marriages was more complete than the ascertainment of relationship between partners of matings of varying legal status in the abnormal series. This makes for a real difference greater than the apparent one. The absence of figures from Götaland for the incidence of first cousin marriages in rural districts with a more mobile population leaves the possibility open that such unions are less common in the eastern region defined by *Bergsten*.

Evidence was produced that homozygosis for recessive genes was

responsible for the mentally defective state of an appreciable proportion of the institutional inmates. This evidence included the observation of clinically well-defined abnormalities known to be caused by recessive genes. To this class belonged 24 matings with offspring having phenylketonuria, 3 of these matings were between first cousins. It was also found that 215 of 1,767 (10.1 per cent) rural matings between unrelated partners, not known to be mental defectives, produced several mentally defective children. This was true of 9 of 37 (24 per cent) first cousin matings between rural residents. For urban matings the figures were 109 of 1,252 (8.7 per cent) and 4 of 13 (31 per cent) for unrelated parents and first cousins, respectively.

Thus consanguineous matings from rural districts seem to be represented in direct proportion to their occurrence in the general population, and, in addition, a fraction of the resulting progeny show recessive abnormalities.

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MONGOLISM IN TWIN SIBSHIPS

By G. ALLEN and F. J. KALLMANN

The dependence of mongolism on maternal age is well established. Less certain, though widely accepted, is its association with maternal ill health preceding or during gestation. Much of the evidence for this association is related to the maternal reproductive system, notably impaired fertility and a history of frequent abortion. For all causes of mongolism,

the common denominator may well be a dysfunction of the maternal endocrine system, especially the ovary. It has been inferred that the given dysfunction is present at the beginning of the pregnancy [4] and produces its effect before the ninth week of embryonic development [8].

Clinically, it is almost impossible to distinguish between influences acting on the ovum or zygote before cleavage and those acting on the early embryo. Vaginal bleeding early in pregnancy may be a sign of deleterious influences affecting the embryo's development, but it may also indicate that the ovum was formed and liberated in an abnormal ovarian environment. The long period of enforced sterility which often precedes the conception of a mongoloid child suggests an abnormal ovary more strongly than an abnormal uterine environment.

Comparative twin studies are certain to furnish valuable information about the etiology of mongolism, provided a representative sample can be collected [3]. An attempt in this direction has been made in our New York State series of 38 mongoloid twins. If an adverse maternal environment is responsible for mongolism, the time and mode of action of this factor are of central importance. More specifically, clarification is needed as to whether or not a mongoloid child ever has a normal one-egg twin partner, and whether the two-egg cotwin of a mongoloid is more likely or less likely to be affected than are full siblings born to the same mother in subsequent pregnancies. Other important questions pertain to the possibility of an altered mongolism risk in twin pregnancies, and the possible occurrence of mongoloid stigmata in the cotwin of a mongoloid.

The *pertinent statistical data* regarding the size and composition of our sample of mongoloid twin index cases are summarized in table 1. In the institutional series (31 cases), four concordant pairs are represented by two index cases each, the given twin partners having been ascertained together.

Table 1. New York State sample of mongoloid twins

Zygosity	Institutional cases		Clinic cases		Total
	Concordant	Discordant	Concordant	Discordant	
One-egg	2	0	4	0	6
Two-egg {	Same Sex . . .	0	0	2	8
		6			
{	Opposite sex . .	0	0	1	15
Undetermined zygosity .	6	3	0	0	9
Total	8	23	4	3	38

Similarly, the clinic cases include two concordant pairs formed by four of the seven twin subjects in this group. In three concordant same-sex pairs, the death of one or both twins interfered with adequate zygosity determination.

Of the 14 cases from same-sex pairs with a clearly established zygosity diagnosis, three pairs (6 cases) are monozygotic and concordant, eight pairs dizygotic and discordant. Since all opposite-sex pairs (15 sets) are discordant our sample of 23 two-egg pairs contains no pair concordant as to mongolism. Conversely, no one-egg pair in this series is discordant.

Another distinctive feature of our sample is an apparent excess of opposite-sex pairs among the two-egg twins. While the observed excess falls short of statistical significance, it is contrary to the trend reported in the literature. In general, it appears that the frequency of opposite-sex pairs is likely to be underestimated, except under conditions of complete ascertainment. According to present concepts of mongolism, however, there is no reason to expect inequality in either direction in a fully ascertained sample. Obviously, therefore, this problem warrants further investigation.

For determining monozygosity in the present sample (fig. 1), blood group data were supplemented by a quantitative dermatoglyphic analysis, and by comparison of ear lobe form and pigmentation of hair and eyes. Other morphologic traits or metric characters cannot be relied upon in twins discordant for a grossly pathologic condition. In same-sex pairs found to be similar with respect to the major ABO and Rh factors, blood typing was continued until a difference appeared or until all available antisera had been tried.

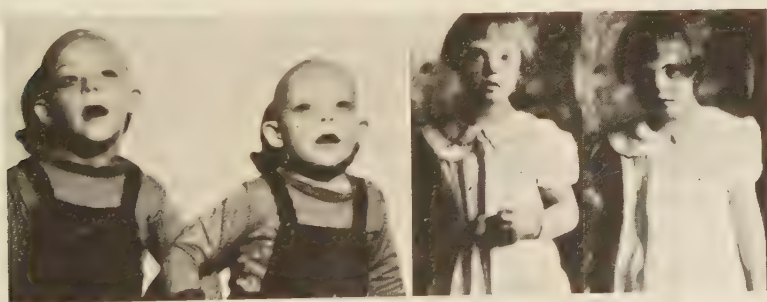


Fig. 1. Two monozygotic pairs concordant as to mongolism.

In analyzing the fingerprints of twin partners discordant as to mongolism (fig. 2), one expects some differences to be related to specific patho-



Fig. 2. Dizygotic twins discordant as to mongolism.

logic changes in the mongoloid twin [6]. However, compared with the usual intra-pair differences in two-egg pairs, statistical abnormalities of mongoloid fingerprints are not sufficiently pronounced to preclude the use of ordinary zygosity criteria, especially in concordant pairs.

Of the three measures used in the analysis of fingerprints, the simplest one is the sum of the homolateral ridge-count differences [7], a difference of more than 40 being strongly suggestive of dizygosity. In *Wendt's* individual pattern score or "Musterwert" [14]—a measuring device of almost equal simplicity—each pattern is classified according to fairly objective criteria and scored from one to seven. A difference of more than five in the twins' total score is strongly indicative of dizygosity. The same diagnostic significance applies to scores over two obtained with *Slater's* discriminant function [13]—the most complex test devised. A *Slater* score below minus one is usually indicative of monozygosity.

The frequency with which dizygotic cotwins of mongoloids may be afflicted with the same condition is still a matter of conjecture. No concordant pair on record has been proved dizygotic by a difference in sex or blood antigens. While the literature contains data on four pairs usually referred to as dizygotic, only one of them is acceptable as such with some assurance [11]. For future research reports in this area it would seem desirable, as has been done in the present sample, to substantiate the zygosity diagnosis by dermatoglyphic and hematologic data and, when these criteria fail, to resort to reciprocal skin grafts. The conspicuous difference

between rejected and successful skin homografts is shown in fig. 3. It will be noted, however, that initial takes in two-egg twins may last three to four weeks.



Fig. 3. Unsuccessful skin grafting in discordant dizygotic pair (compared with one-egg pair).

Before concordance rates are discussed, it is advisable to determine the relative frequency of mongolism not only in institutionalized twins and non-twins, but also in the two types of twins. The improbability of twins

Table 2. Admissions to state schools 1947-1954.

Diagnostic group	Total admissions		Reported twins		Proportion of twins in per cent
	Number	Per cent	Number	Per cent	
Undifferentiated and familial	7,597	62.9	197	59.2	2.59
Mongolism.	1,177	9.8	23	6.9	1.95
Cranial anomaly	741	6.2	21	6.3	2.83
Cerebral palsy	596	4.9	23	6.9	3.86
Post-traumatic	797	6.6	40	12.0	5.02
Miscellaneous	1,158	9.6	29	8.7	2.50
Total	12,066	100.0	333	100.0	2.76

being more susceptible to mongolism than singletons can be inferred from the figures in table 2. Among all admissions to New York State schools for mental defectives, there were 9.8 per cent mongoloids in the total population, and 6.9 per cent in the known twin population. The frequency of twins among mongoloid admissions is only 1.95 per cent. Hence, while the observed frequency is a little lower than that for mental defectives in general, it is close to the frequency of 1.9 per cent expected in the general population after the age of one year [1].

In view of the well-established increase in the number of twins born to older mothers, the point may be raised that the expected twin frequency of 1.9 per cent is not strictly applicable to mongoloids. However, according to the statistics and computations in table 3, there is only a small difference between the twin rate for the general population and that for mothers with an age distribution observed in mongolism. The expected total twin rate for all births is 11.02 per 1000, as against a figure of 12.61 per 1000 for mongoloid births.

Table 3. Distribution of mongoloids, twins, and mongoloid twins by maternal age

Maternal age	Twin pairs per 1000 deliveries		Expected distribution of mongolism	Expected twin births in 1000 mongoloids		
	Same sex	Opposite sex		Same sex	Opposite sex	Total
Under 20 . .	4.71	1.48	27	0.13	0.047	0.17
20-24 . . .	6.92	2.02	120	0.83	0.24	1.07
25-29 . . .	7.84	3.57	162	1.27	0.58	1.85
30-34 . . .	8.69	4.47	184	1.60	0.82	2.42
35-39 . . .	10.34	5.26	268	2.77	1.41	4.18
40 and over .	6.67	5.56	239	1.59	1.33	2.92
All ages . . .	7.67	3.35	1000	8.19	4.42	12.61

Another aspect to be considered is that twinning results from abnormal processes in the mother or in the zygote, and exerts abnormal influences over at least the later stages of gestation. It would seem, therefore, that the absence of any evidence for an increased twinning rate in mongoloid pregnancies has etiologic implications. If any major factor were common to both mongolism and twinning, or if either condition tended to cause or preclude the other, a definite discrepancy in twin frequencies would be expected.

Actually, the relation between maternal age and mongolism follows an entirely different frequency curve from that for the relation between maternal age and twinning. It may be concluded, therefore, that the mutual dependence of mongolism and twinning on maternal age is largely coincidental. Since there is no apparent etiologic connection between mongolism and twinning, any evidence obtained from twins on the nature and causation of mongolism may be assumed to apply to mongoloids in general.

As to the question of mongoloid stigmata in otherwise normal relatives, it can be stated that no statistically significant mongoloid tendencies were found in 18 dizygotic cotwins of our sample who were compared with their sibs. The analysis [2] covered a variety of quantitative and qualitative traits, with emphasis on intellectual performance, head measurements and dermatoglyphics. Obviously, if subclinical manifestation of this kind resulted from intrauterine influences, they would be most strongly expressed in the cotwins of mongoloids. In contrast, if such stigmatizing features depended on genetic factors, they would be expected to appear equally in cotwins and sibs.

The results of the dermatoglyphic part of this analysis are presented graphically in fig. 4. They leave no doubt that at all points where mongoloids deviate significantly from normal, the unaffected cotwins closely resemble the normal sibs, rather than the mongoloids. In regard to all three criteria used, the observed differences between affected and unaffected members of

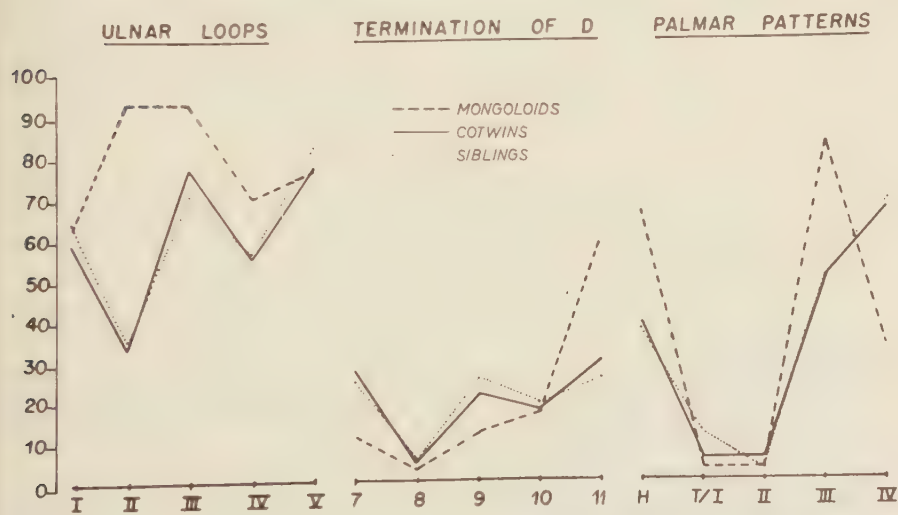


Fig. 4. Comparative dermatoglyphic findings in mongoloids and their cotwins and siblings.

index pairs are consistently large, two of them at the one per cent level of confidence.

On the whole, it is indicated by our data that if intrauterine conditions produce mongolism in one member of a two-egg pair, they do not ordinarily bring about changes in the cotwin that could be regarded as partial mongolism. In effect, this finding supports the prevalent view of mongolism as a disorder of development that follows *en bloc* from an early deviation. The absence of mongoloid stigmata in the dizygotic cotwins of mongoloids and the entirely different concordance rates for the two zygosity groups seem to point in the direction of the etiologic views expressed by *Penrose* [12]. The essence of his concept is an interaction of embryonic and maternal abnormalities.

The observed concordance rate for one-egg twins is so high that it is best explained along one of the lines of reasoning advanced by *Jenkins* or *Penrose*. One plausible explanation originated by *Jenkins* [9] is that the maternal influence acts decisively on the growing ovum or on a very early stage of the embryo, but in a sporadic manner, perhaps involving a threshold which is rarely passed. Another possibility is that a pathologic response to an abnormal intrauterine environment is determined by the genotype of the embryo at whatever stage the environment exerts its effect.

In contrast to the monozygotic concordance rate, the observed concordance in two-egg twins agrees so well with the expectancy of mongolism reported for sibs born after a mongoloid, that a mother's potential to produce mongoloid children, once established, may be assumed to remain approximately the same. According to *Böök* and *Reed* [5], the morbidity expectancy is 3.9 per cent for sibs born after a mongoloid. The only estimate available for dizygotic cotwins [2] is 4.5 per cent with an upper limit of 5.2 per cent. Hence, the maternal factor operating in the etiology of mongolism is to be sought not in some event or transient state associated with the mongoloid pregnancy, but in a more or less permanent change that has occurred in the physiology of the mother's reproductive or endocrine system.

In summary, the findings obtained from our consecutive series of 38 mongoloid twins are as follows:

(1) There is no evidence for an etiologically significant connection between twinning and mongolism.

(2) The morbidity risk in one-egg cotwins of mongoloids is close to 100 per cent. The corresponding rate for two-egg cotwins does not seem to exceed that of their later-born sibs, which is approximately four per cent.

(3) With respect to intelligence and physical stigmata of mongolism, no significant abnormality was found in 18 dizygotic cotwins of the index cases. For all traits studied, the cotwins and sibs proved to be similar within the limits of sampling error.

(4) As to the etiology of mongolism, our conclusion is that susceptibility to this condition is determined at the very start of development in either the cytoplasm or the genes of the zygote. Apparently, the immediate cause is traceable to some more or less permanent change in the mother's reproductive or endocrine system, and not to a transient noxious influence.

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Discussion

P. J. Waardenburg (Leiden): If hormonal disturbances in the mother are the cause, I wonder why mongolism is not more frequently present in siblings and especially in both dizygotic twins. If a dysplasmatic egg cell were the cause it hardly explains why mongolism is such a distinct complicated entity or syndrome that repeats itself in such a stereotyped way in all cases and that no other anomalies arise in that way. I agree, therefore, with Professor Kallmann when he assumes a combination of genotypical and environmental influences. I considered the possibility of chromosomal aberrations years ago.

S. C. Reed (Minneapolis, Minnesota): If there is a shortage of twins, one or both of whom are mongoloid, it might be the result of the heart defect which so often is a part of the Mongolism syndrome. The early death in utero of one of the twins would result in the survivor being recorded as a single birth.

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STUDIES IN THE ETIOLOGY OF MONGOLISM

By J. ØSTER

In recent years an investigation has been carried out at the University Institute for Human Genetics, Copenhagen, for the purpose of throwing light on the etiology of Mongolism. By collecting information from the lying-in departments and all hospitals, mental institutions, and practitioners, within a certain, delimited part of Denmark, we succeeded in getting a sufficiently large unselected material. It was possible to register 1006 Mongols, 526 of whom were alive at the time the investigation took place.

It may be mentioned that the total of 526 living Mongols, which constitutes the basis of the present investigation, has been examined by me, and I have also been in personal contact with the parents, and have collected the genealogical information as well as information concerning the condition of the mother before, during, and after the pregnancy which resulted in the birth of the Mongol.

As to the incidence of Mongolism among new-born it was found that there was 1 Mongol among 618 live births, and although this must be considered as a minimum figure, I have worked with this probability in the calculations which follow.

It appears from my investigation—as has been found in previous etiological studies—that there is a clear tendency towards a considerably higher age for mothers giving birth to Mongols than for mothers giving birth to normal children. The average age for the mothers at the births of the Mongols was 35.1 years. The average age for parturient mothers in the Danish population is 28.7 years.

On the assumption that there is 1 Mongol among 618 live births, and as we know the percentage distribution of mothers of Mongols and of child-

bearing mothers in Denmark at the age of delivery, it is possible to calculate the percentage incidence of Mongol births for the various age groups. The incidence among mothers 15–19 years old is 0.061 %, and is then steadily increasing to the age group 45–49, where the greatest incidence, 1.78 %, is found in the present material.

After the births of the 526 Mongols, the mothers of these have had a further 354 live births, 4 of which were Mongols. Because of the higher age of the mothers of the Mongols, a somewhat greater incidence than 1 Mongol for each 618 live births must be reckoned with. As mentioned the greatest incidence in the present material is found in the age group 45–49 years, 1.78 %. The incidence of yet another Mongol among siblings (4 among 354 live births) gives 1.1 %, i.e. almost the same order of magnitude.

Through statistical investigation an upper limit to the anticipated incidence of a Mongol birth among these 354 live births can be found, on the assumption that the 354 live births after the Mongol births are born with the same incidence, independent of the age of the mother, from the time of the Mongol birth and up to the age of 50; then they will be distributed according to the age of the mother at the birth in the same way as the number of years lived. This incidence which, with the assumption made, must be an upper limit is found to be 0.89 %. $4 \text{ in } 354 = 1.1 \%$ does not deviate significantly from this. In the material presented it has not been possible to demonstrate any familial accumulation among siblings.

In his recent book "Counseling in Medical Genetics" *Sheldon C. Reed* has criticized this calculation as follows, "However, this estimate of 0.89 % is based on the assumption that the children subsequent to the Mongoloid child were equally distributed over the years from the birth of the Mongoloid to the time the mother reached 50. But an even distribution of the children over these ages would not occur; consequently a bias of considerable magnitude has been introduced into the calculation of the 0.89 %. The correct expectation should be 2 or 3 fold lower". *Reed* came to this conclusion statistically by distributing the 354 births after the propositus according to normal distribution of births after the age of mothers in Denmark; but also according to this calculation it is impossible to say whether one arrives at a correct figure.

As the crucial point is the fact that these calculations are based on assumptions, the validity of which can be questioned, I have collected information of the age of the mothers for all births both before and after the Mongol. In this way it should be possible to reach an exact estimation of the expected frequency of a further Mongol among the siblings. As a result of this revision of the material it is calculated that the expected

number of Mongols among the siblings after the *propositus* is in all 1.41. 4 Mongols were found in all. The probability of finding as many or more by comparison with the expected number is according to the Poisson-distribution $P = 5.5\%$. It is therefore not significant, even though the probability does not lie far from the 5% limit. I have also investigated whether the Mongol births among all the siblings, but without the *propositus*, were more frequent than expected. According to the procedure of the *propositus* method, 7 have been found among all siblings, and the expected number is calculated as 3.48, which gives a probability of 6.5% . There is therefore no significance present here either.

From this investigation it is also clear that there is a shift in the direction of mothers of Mongols giving birth to children at quite an advanced age; consequently it is unrealistic—as *Reed* has done—to assume in the calculations that the births of children following the Mongol were distributed in the same manner as births are otherwise distributed in the Danish population according to the age of the mothers.

As to diseases and defects in relatives of Mongols it was found as a result of the genealogical investigation on about 10,000 near relatives to the *propositi* that there was no evidence to support the view that Mongolism or other forms of mental deficiency, neuro-psychiatric diseases or congenital defects are particularly frequent among the relatives of Mongols.

As to the etiological significance of maternal factors I have mentioned the advanced age of the mothers at the births of the Mongols. In addition I found a relatively greater number of long intervals between the time of marriage and the first pregnancy in the cases where this resulted in a Mongol. Likewise it was possible to demonstrate a significantly longer pregnancy-free interval before and after the Mongol than between normal births with the same birth order. The longer interval before the Mongol must be biologically conditioned at any rate. It further appeared that the Mongol is not in general the last in a large family of children. Surprisingly many were the first to fourth in the family. All these factors mentioned tend in the direction of reduced reproductive faculty in the women in question, I think. But this is hardly due to incipient climacterium, which was only found in 5.4% of the mothers at the time the conception of the Mongol child occurred.

It was also striking that in the period around the Mongol pregnancy (3 years before and 3 years after) an accumulation of diseases was found in the mothers, and approximately 15% of the mothers in this period underwent curettage. It was also remarkable that after the Mongol birth there was a significantly higher frequency of abortion (16.5%) than before (9.7%).

The pregnancies which led to the births of the Mongols offered nothing significantly abnormal.

As a conclusion it may be said that it has not been possible to find supporting evidence for the idea that Mongolism might be a hereditary disease. There is no indication for eugenic precautions in the case of women who have had a Mongol child once; their risk of having yet another Mongol child is not significantly greater than the risk for other women in the same age group. The advanced age and the demonstrated depressed reproductive faculty of the mothers of the Mongols suggest that these women are in a condition of biological insufficiency, brought about by causes as yet unknown. It would be desirable if a more thorough evaluation of the hormonal metabolism of these older women could be carried out.

From the present investigation it is impossible to state anything as to the frequency of Mongolism throughout the years. It might be anticipated that the frequency in the population is increasing on account of the use of chemotherapeutics and antibiotics in the treatment of infections. At the same time, however, voluntary birth control reduces the birth rate in the older age groups in particular. In Denmark, during the period from 1901 to 1940, the number of women over 35 having children was reduced from 23.1 % to 15.5 %. If such a development continues, a reduction in the frequency of Mongolism can be expected; it appears from my investigation that 30 % of the Mongols could have been avoided if the women in question had avoided having children after the age of 40 years.

Further remarks and documentation will appear in the "Danish Medical Bulletin" 3, 158, 1956 ("The Causes of Mongolism").

Discussion

S. C. Reed (Minneapolis, Minnesota): Dr. Øster has been most kind and generous in his comments about the statistic change in method suggested for his study of Mongolism. This is a small detail and does not need further attention. I would be very much interested to know what Dr. Øster thinks about the twin data for Mongolism, both those in the literature and the very clear results just presented by Drs. Allen and Kallmann.

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MICROCEPHALY IN THE NETHERLANDS

By J. van den BOSCH

Microcephaly has long been an object of interest. Not only as a conspicuous abnormality in man, with the extreme form of mental deficiency and the typical form of the head, but also because of the fact, that the mode of inheritance of the genetic form presents such interesting features, which give insight into the complexity of several problems of human population-genetics. Recent studies by *Böök*, *Schut* and *Reed* and *Taku Komai* et al., have inspired the Department of Human Genetics of the Netherlands Institute for Preventive Medicine in Leyden to investigate the occurrence of this abnormality in a third country, the Netherlands.

The Netherlands, we thought, could prove to be an ideal object for investigation, because of the following considerations:

- (1) It seemed possible to trace a high percentage of all living microcephalics, because under the social conditions in our country the severe mental defect nearly always leads to admission to an institute for mental defectives or other asylum. Also admission at a rather early age could be anticipated. These two considerations seemed to justify the expectation, that practically all living microcephalics from the age of 5-10 years onwards could be traced. We were, however, able to trace four microcephalics during the frequent field-work expeditions, during 1954 and 1955, who were microcephalic on an undoubtedly hereditary basis and who were still living with their families, but in three of these cases, sibs, this fact was due to the exceptional pedagogical capacities of the normal parents and we feel justified in anticipating that these three children will at some time, probably after the death of the parents, have to be admitted to an institution, like three microcephalic brothers, who presented too many difficulties in the family surroundings even for these capable parents. The fourth

microcephalic, who also was traced as a secondary case during our genealogical researches, has not yet attained the age of puberty, though it must be said, this his chances of keeping out of an institution appear favourable.

- (2) The Netherlands are a small country, every corner of which can be reached by road within a few hours with Leyden as starting point. This together with the fact, that we knew, that microcephaly of hereditary origin could be expected to be very rare in our country as in others, seemed to present an acceptable basis for an investigation, which would have to be made by a very small team: as a matter of fact all field-work was done by myself, the registration and correspondence was done by my secretary, the genealogical research, especially of the earlier generations, was carried out by a professional genealogist.
- (3) The fact, that registration of births, marriages and deaths has been compulsory since 1811 and the very good condition in general of the old Church registers and registers of notarial acts in our country promised to be a very effective tool in our search for consanguinity among the parents of the microcephalic probands. This consideration was very important, as we intended to use the occurrence of consanguinity as evidence (in combination with other terms) for the hereditary origin of a case.

Although collecting the data was relatively easy, its analysis was more difficult: Our country, small though it is, does not present one population in the strict sense of this word: as a matter of fact the 10.5 million people, inhabiting our country, are divided into many different groups: this division has both religious and geographical causes. Most of the ca. 30 % of the Roman-Catholics e.g. live in the provinces North-Brabant and Limburg; this fact implies, that consanguineous marriages up to a certain degree are strongly discouraged by the R.C.-clergy; at the same time this leads to a more frequent occurrence of consanguinity of a more remote degree, especially in such parts of these provinces, which may be considered as isolates in virtue of their geographical or social position. Nor can the Protestant part of the Dutch people be regarded as a population with e.g. a reasonable amount of panmixia, divided as they are into at least five different religious groups, which practically do not intermarry. This would not be a very serious difficulty, if these five groups were at the same time living in five different districts. This is not the case at all: they are spread all over the country and the large cities. Even the population of an island like the island of Texel with 10,000 inhabitants, whose forefathers have

been isolated from the mainland for several centuries, are the progeny of at least three different religious groups, which show but little intermarriage.

It is clear that Dahlberg's formula for estimating the gene-frequency cannot be applied, as the percentage of first-cousin-marriages in the population is not representative of the real degree of inbreeding. Nor was it possible to make calculations with Wright's coefficient of inbreeding, as the value of this coefficient for the Netherlands or for the districts under observation is unknown.

The best approximation for the incidence of the gene in the Dutch population could be obtained by the sibships, in which microcephalics were born in four large cities with a total population of 2,333,346. Consanguinity could not be found as far back as 6-8 generations between any of the parents of these microcephalics and it seemed permissible to assume a fair amount of panmixia in these cities, at least a mean coefficient of inbreeding smaller than 0.001. Calculating on these grounds, we found a frequency of the gene for microcephalia vera of 1/536. In 8 rather isolated rural municipalities, where microcephalics were born, the gene appeared to be about 10 times as frequent.



Fig. 1. Microcephaly in the Netherlands. Estimates of the gene-frequency in 4 cities and 8 isolates.

In the map (figure 1) the thinly drawn circles indicate the cities of Amsterdam, The Hague, Rotterdam and Utrecht, the accentuated ones are the isolated districts just mentioned.

Table 1 contains the same findings in table-form.

Table 1. Estimates of the frequency of the gene for Microcephalia vera in the Netherlands

I	Total population (10.435.631)	$q = 1/477$
II	Amsterdam Rotterdam Den Haag Utrecht (2.333.346)	$q = 1/536$
III	In 8 isolates: Huissen Etten Lemmen Elst Putten Didam Hardinxveld Enkhuizen total population 68.427	$q = 1/35$ $q = 1/66$ $q = 1/38$ $q = 1/40$ $q = 1/35$ $q = 1/55$ $q = 1/50$ $q = 1/61$
IV	Mean of 8 isolates	$q = 1/45$

In table 2 a comparison is made between the estimated gene-frequencies in Japan, Sweden and the Netherlands. These estimates, though based on different data and different methods of calculation, show agreement in their order of magnitude. As the Dutch material consisted only

Table 2. Estimates of the frequency of the gene for Microcephalia vera in three different countries

	q	Authors
Japan. . .	$1/159 - 1/249$	<i>Komai, Kishimoto and Ozaki</i> (1954)
Sweden . .	$1/158 - 1/230$	<i>Böök, Schut and Reed</i> (1953)
Netherlands	$1/477$	<i>Van den Bosch</i> (1955)

of microcephalics, who were alive in 1953 and between the ages of 5 and 55 years, it may be that our estimation gives too low a figure. On the other hand, this fact may well be compensated by the not-calculated coefficient of inbreeding, which, though probably smaller than 0.001 in the total population, is certainly higher in different districts.

The total percentage of consanguinity among the parents of microcephalics was 70.58%. The percentage of first-cousin-marriages was 23.52%. One of the microcephalics was the product of incest between brother and sister. The pedigree shows, that this is not the only consanguinity in this family: the parents of the brother and sister being first cousins.

The sex-ratio, 23 boys:8 girls, in our material, is in agreement with the findings of *Penrose* and *Komai*: the probability that this deviation from the normal 1:1 ratio is due to chance is less than 1%.

I want to finish with what is perhaps the most important result of our investigations: the fact, that at least in the Dutch population one is not justified in speaking of "the frequency of the gene for microcephaly", as if it were evenly distributed over the whole population. It is necessary to calculate the frequencies in the different districts with their different coefficients of inbreeding. In this way splitting up our country in districts with relatively very high and low frequencies of the gene not only for microcephaly, but also for other more important recessive diseases, we might be able in the future to arrive at better founded genetic counselling, not only in individual cases, but also in preventive medicine in general: the inhabitants of districts in which too many homozygotic recessive children are born as a result of too much inbreeding and too high a frequency of the gene in question may be spared much misery by instruction about the ways in which they can avoid abnormal offspring, breaking down of isolates! It is true, that this breaking down will lead to a higher frequency of heterozygotes in the total population and thus give every member of the population a greater chance of carrying a recessive "abnormal" gene. Yet I believe, that the physician, who has specialized in the field of human genetics and who wants to be regarded as a practitioner in the first place, should occupy himself primarily with the question within his immediate reach: how can I avoid grief for my fellow-men, who don't ask my advice about the health of the population of my country in the (sometimes very remote) future, but about the health of their immediate offspring.

HEREDITY AND VARIATIONS IN NORMAL AND ABNORMAL BEHAVIOUR PATTERNS

Fuller, J. L.: Acta genet. 7, 403-407, 1957

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COMPARATIVE STUDIES IN BEHAVIORAL GENETICS

By J. L. FULLER

Human genetics now stands on its own feet as an independent discipline no longer dependent upon principles derived from the study of inheritance in *Drosophila* or the house mouse. Progress in psychological genetics has lagged behind advances in the analysis of physical traits. The choice of traits for study, their definition and quantification present problems which must be resolved before genetical studies are profitable. Most psychological traits are highly environment sensitive, and hereditary determinants are hard to isolate unless environmental factors are controlled more rigorously than is possible in man. For these reasons psychological genetics may continue to profit from close association with experimental work on animals. I have selected five principles which may be extracted from such research over the past few years, and shall attempt to relate them to human psychological genetics.

(1) Heritability of behavioral characteristics is not an exceptional situation, but is practically universal.

Two kinds of research support this principle: (a) Isolation of behaviorally distinct strains by selection based on behavioral criteria; (b) comparisons between the behavior of genetic strains not particularly selected for the trait under consideration. Both cognitive aspects of behavior (problem solving), and motivational aspects (hunger and sex drive, timidity, hoarding and the like) appear susceptible to genetic influence. Perhaps because the intellectual development of laboratory animals is so low, it is usually easier to demonstrate hereditary differences in motivational and affective traits than in intelligence.

So wide-spread are the relationships between heredity and behavior that I know of no properly designed selection program which has been

unsuccessful, nor do I know of any extensive sampling of strains which has failed to find behavioral differences which can be reliably measured.

(2) A gene may produce extensive effects upon behavior which are not related in any known manner to the organic effects of the gene.

This principle is best illustrated in *Drosophila* where genes for eye color, body color, bristle structure and the like have been found to affect rate of wing vibration, strength of mating drive and rate of photokinesis. The situation is not as clear when one considers higher animals in whom learning is of greater importance. Claims that single gene substitutions produce important differences in behavior without producing a sensory, neural or muscular deficit cannot be accepted on the basis of available data. Where such deficits are found it is possible to divide the research problem into two parts: (a) a genetic portion concerned with the mode of inheritance and the embryology of the defect, and (b) a psychological problem dealing with the influence of the defect upon behavior.

In spite of the difficulty of demonstrating the psychological effects of many mammalian genes, I believe we must admit the possibility that every gene substitution involves some change in the organism which could have psychological consequences under certain conditions. Better experiments must be done before this can be asserted with complete confidence.

(3) The polygenic models developed by *Wright* and *Mather* provide reasonably satisfactory descriptions of the inheritance of behavioral traits.

Two models have been tested in our laboratory one applicable to characters which vary continuously, the other to characters of discontinuous expression.

For example *Thompson* and *Fuller* measured activity in hybrids between an active (C57BR) and an inactive (A) strain of mouse. When scores for activity were transformed to a new scale (the square root of the raw activity scores), the variances of the high and low strains were substantially equalized. The means of the hybrids on this transformed scale fell into the expected orderly sequence, and the variances of the backcrosses and F_2 were increased as predicted from the laws of segregation. Similar computations applied to data collected several years ago by *Dawson* on inheritance of running speed in mice were also reasonably successful.

In the second type of model we have combined the polygenic scheme with the concept of thresholds. This has been used to describe the inheritance of susceptibility to sound-induced convulsions in mice. The trait had been reported to be dependent upon a single Mendelian dominant. The essence of the model is the concept of an array of genotypes which vary in mean

susceptibility from zero to one hundred per cent. In the middle of the array, the mean risk is 50 %. Environmental factors affect the development of all genotypes, but those near the 50 % risk point will be most sensitive to the external milieu. Genotypes of the extreme classes will be environment-stable.

Models of this type are extremely flexible, and have, I believe, great power for prediction and explanation. Unfortunately I know of no adequate consideration of such a system with relation to population genetics. The mathematical treatment appears to this non-biometrician to be complex, but he has faith that there are individuals who could deal with it. Even without this extension of the theory, we may conclude that quantitative biometrical genetic methods can be applied to psychological characteristics as well as to body measurements.

(4) Most behavioral traits studied in animals are specific rather than general.

As an example we may consider Tryon's maze-bright rats obtained by selection. These animals were inferior to his maze-dull strain on some learning tasks. Positive intercorrelations were marked only on tasks very similar to the primary criterion of selection. Our own work on behavioral differences in various pure-bred dogs confirms this. No general factor similar to *Spearman's G* emerges from the study of the inheritance of animal intelligence.

There are at least three possible explanations of this fact. (a) General intelligence in man may be a psychological artifact produced by assortative mating between individuals high in diverse abilities. This suggestion was made years ago by *Bartlett* and by *Price*. (b) General intelligence may involve a level of concept formation unique to man, and not found in animals with a simpler cerebral cortex. (c) Animals may have a general intelligence factor which experimental psychologists have not been clever enough to identify.

Whatever the explanation may be, it is certain that the greatest success in animal work has been obtained when specific behavior items, even specific movements have been utilized as traits for investigation. A component theory of behavior is required to fit a particulate theory of heredity.

(5) Animal studies have provided some clues to the nature of the relationship between gene substitution and behavioral variation.

Recent theories in general emphasize central rather than peripheral effects of genes. *Young* and his co-workers have found that the strength of the sex-drive in male and female guinea-pigs of different strains is associated with sensitivity to steroid hormones rather than to the rate of

hormone production. The target organs through which androgens and estrogens arouse sex-drive are presumably in the brain.

Fuller, Rosvold and Pribram found that amygdalectomy produced greater changes in the aggressive behavior of wire-haired terriers than the same operation produced in beagles. The data are compatible with the theory that selection for aggressiveness in terriers has operated upon this particular brain nucleus.

Fuller and Jacoby have studied the strength of food drive under different conditions in genetically obese mice. Fat animals acquire fat because they eat more per unit of body weight than their normal siblings. However, the reverse may be true if the diet is made unpalatable. Both kinds of mice vary their food intake according to palatability, but the normal mouse has a built-in calorie regulator which can exert physiological (or psychological) dominance over unpleasant sensory impulses.

Sound-induced convulsion susceptibility has also been investigated in our laboratory. Mice of various strains are placed in an enclosure and exposed to the sound of a door-bell. Some are merely startled; others have a running fit terminated by a violent tonic convulsion. As stated before various inbred strains differ markedly in susceptibility to a standard test situation. We have attempted to explain susceptibility and resistance in terms of the relative rates of recruitment and blocking of neural pathways. Our idea was that the organism as a whole behaved like a spinal cord preparation with greatly elongated time constants. If the rates of neural recruitment and inhibition were inherited independently, we believed we could explain the differences between strains with respect to susceptibility risk, and concomitant differences in mean seizure latency.

In brief, this idea was supported by a series of experiments on pure strains and their hybrids. More recently an enzymatic basis for some of these genetic differences has been suggested by *Abood and Gerard* who found the development of the ATPase system to be correlated with the reduction of convulsion risk. The effective genes may operate through control of the rate of enzyme synthesis in the central nervous system.

Conclusions:

- (1) Most behavioral characters are affected by gene substitutions and most gene substitutions may affect behavior under certain circumstances.
- (2) The inheritance of quantitative behavioral traits is as lawful as the inheritance of physical characteristics.
- (3) Psychological genetics might well increase emphasis on the inheritance of developmental patterns of behavior, and not be restricted to the phenotype at one particular age.

(4) Dynamic response tests should be used for the investigation of constitutional factors affecting behavior whenever possible. The important thing about a hormone, for example, may not be the amount found in the plasma, but the way in which the organism responds to changes in concentration.

(5) Simple behavioral traits should be utilized as much as possible in building up a science of psychological genetics. Techniques such as factor analysis may help to define such traits.

The student of animal psychological genetics has some advantages in his ability to utilize classical methods of genetic investigation not available to his colleague working on human problems. However, we must always bear man's psychological uniqueness in mind as we extend the results of comparative research to humankind. We must avoid the error of oversimplifying man. But we must also avoid the error of not recognizing the biological basis of many human drives, and the genetic basis of human biology. Both branches of the science will profit from interchange of information and ideas.

Spindler, P.: Acta genet. 7, 407-408, 1957

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EINE HOMOLOGIE DES VERHALTENS BEI MENSCH UND SÄUGERN

(Zur Vererbung von Verhaltensweisen)

Von P. SPINDLER

Nicht nur die morphologischen Anlagen, sondern auch das Verhalten des Menschen sind erblich und haben sich phylogenetisch entwickelt. Die Ergebnisse der Vergleichenden Verhaltensforschung (Ethologie) sind auch auf Verhaltensuntersuchungen beim Menschen anzuwenden.

Mit Hilfe der Zwillingsforschung kann man bereits menschliche Verhaltensweisen auf ihre Erblichkeit untersuchen. Die in ihrer Form wenig modifikablen Instinktbewegungen sind für erbbiologische Analysen am besten geeignet.

Bei einem akustischen Schreckreiz war es dem Verfasser möglich, eine bei erbgleichen und erbverschiedenen Zwillingen (EZ und ZZ) gleichartige Bewegungsweise festzustellen: Unmittelbar nach dem akustischen Schreckreiz wird der Hals eingezogen und beide Schultern hochgenommen, der Kopf nach vorne gesenkt und die Augenlider geschlossen sowie die Mundwinkel nach auswärts verzogen («Hals-Schulter-Reaktion»). Dieses Verhalten konnte auch bei einer Reihe von Säugetieren nachgewiesen werden (Igel, Brauner Bär, Malaienbär, Dingo, Schakal, Fuchs, Gnu, Wildschwein, Zebra, Löwe, Tiger, Löwe-Tiger Bastard, Panther, Puma, Vielfraß, Schimpanse). Es ist der Schluß naheliegend, daß die «Hals-Schulter-Reaktion» eine dem Menschen und den Säugern *homologe* instinktive Verhaltensweise sein dürfte.

Bei der Reaktion auf einen akustischen Schreckreiz konnten beim Menschen zwei voneinander deutlich unterscheidbare Verhaltensweisen beobachtet werden:

1. für alle Menschen gleiche, arttypische Verhaltensweisen (z. B. die «Hals-Schulter-Reaktion»);
2. individuell vererbte Verhaltensweisen (Mitbewegungen, EZ-Konkordanzen bei gleichzeitiger ZZ-Diskordanz u. a.).

Über die funktionelle Repräsentanz dieser Bewegungsweisen im Zentralnervensystem liegen nur erste orientierende Befunde vor.

Die Ergebnisse wurden mit Hilfe von kinematographischen Aufnahmen (64 Bilder/sek.) gewonnen.

Untersuchungen über die Genetik von Verhaltensweisen beim Menschen werden im Anthropologischen Institut der Universität in Wien weiter durchgeführt.

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Beide Filme sind bei der Bundesstaatlichen Hauptstelle für Lichtbild und Bildungsfilm in Wien IX. erschienen und wurden unter der wissenschaftlichen Leitung des Verfassers zu Forschungs- und Demonstrationszwecken hergestellt (16 mm).

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THE RELATION BETWEEN PSYCHOLOGY AND GENETICS

By J. MAXWELL

Psychology may be defined as the systematic study of human behaviour, and is mainly concerned with differences in behaviour. There are differences in categories, such as certain psychotic syndromes, or certain types of mental defect; there are also characters which differ in degree within the range of "normality". Differences in intelligence are of the latter kind, and the paper deals with such differences, examining how far any structure of genetic factors can be discerned in the available data. The term "intelligence" requires exact definition. What in practice are observed are not differences in "intelligence", but differences in scores on an intelligence test. Before any genetic analysis can be made, the properties of these scores need to be known.

The main properties are:

- (a) There is an element of chance in the scores.
- (b) The distribution of scores is made "normal"; no inference can be drawn about the distribution of intelligence in a population.
- (c) Tests are constructed with reference to a particular cultural environment; there is no test of "pure intelligence".

These properties impose certain limits on any genetic interpretation of data obtained from intelligence tests. It is possible to establish both a genetic and a cultural scheme of inheritance, but virtually impossible to disentangle them.

Data obtained from 654 families comprising 1690 children are examined to see how far any indication of the inheritance of intellectual capacity can be inferred. A correlation of $r = .5$ between sibs was observed. This is lower than expectation from a model involving assortative mating and differential

fertility. Correlation between the scores of male/female pairs of twins was higher, but not significantly so. The contradiction between the observations and the model appears to lie in the constitution of the parent population, which seems to be biased. Various possibilities are discussed, but a definite solution seems to be possible only in terms of direct observation of the relationship between the intelligence test scores of parents and their offspring.

Kallmann, F. J. and G. S. Baroff: Acta genet. 7, 410-421, 1957

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HEREDITY AND VARIATIONS IN HUMAN BEHAVIOR PATTERNS

By F. J. KALLMANN and G. S. BAROFF

One of the most auspicious developments in modern psychological medicine has come from the adoption of interdisciplinary research methods for investigating the genetics of human behavior. Released from the bondage of a two-valued system of conceptualization—wherein belief in heredity as a determinant of variable behavior patterns was equated with distrust in man's perfectibility—and ably supported by the equally young disciplines of psychochemistry and psychopharmacology, psychogenetics has finally broken new ground, away from a rigidly codified scheme of dichotomous absolutes. Among the achievements of this "break-through" [11] has been the realization that the concept of interaction of heredity and environment in personality development is formulated as a meaningless antithesis so long as vague abstractions are used in describing the properties of an organism that is most certainly both active and reactive.

Man, to be sure, mirrors his culture and the social configuration of his parental home. Yet he also forms an autonomous functional unit that perpetuates itself as the matrix of his hierarchically organized traits and self-assertive acts. The importance of genic elements in this organizational process rests on the interdependence of organic structure and psychologic function throughout the life of the individual [2, 8, 12].

While environmental influences are vital, they can be effective only within the limits set by the genic constitution of the organism. Beyond these limits, no power plant exists for generating behavioral potentials. Such basic phenomena as growth and maturation, homeostasis and adaptation, reflexive behavior and constitutional strength remain chameleonic allegories without the solid foundations of genetic principles.

In order to maintain his present evolutionary level, man must be both conditionable by culture and impressible by education. The ability to learn from others and profit from experience is determined by the genotype, while cultural values and opportunities have to be acquired by each individual through communication with his group. Variations in basic traits are inherited to the extent that they are end-products of a chain reaction set in motion by genes.

In broadest terms, therefore, a person's phenotype may be defined as the visible expression of his moldability by environmental influences, with his genotype determining his norm of reaction to the total range of environments possible in his lifetime. The implication here is that every gene-controlled mode of activity requires an operational area in which to unfold [13, 14, 19].

Since no part of this environmental area of operation is inert, in the sense of being ineffectual where the behavioral responses of the individual are concerned, it is axiomatic that no type of behavior is controlled entirely by genic elements, nor is it ever the result of a single cause, genetic or non-genetic [3, 4, 21]. Estimates of individual contributions are meaningful only when viewed against the backdrop of the total genetic and environmental variation observed in a population.

Non-instinctive responsiveness to conditioning influences varies in different stages of development, and from person to person at a comparable stage of development [4]. So vast is the aggregate of gene-specific personality constituents, and so infinite the number of interactive variables in the shaping of a behavior pattern, that every individual can count on being unique—identical twins excepted.

The gene-specific uniqueness of man's individuality is now recognized in all branches of the behavioral sciences, even if the parliamentary Bill of Acceptance has yet to be ratified by some. The main differences lie in the descriptive labels affixed to this uniqueness. Many of them are little more than elegant allegories intended to convey genetic ideas in a palatable form [1, 15, 17].

Despite the disparate terms used to describe the interaction of genetic and non-genetic components of behavior, there is interdisciplinary agree-

ment on at least one general premise; namely, that those aspects of the environment which are potent in affecting the individual depend not only on the degree of maturity attained, but also on the inherent capacity for coping with extrinsic hazards. Another point of unanimity is the belief that the interdependence of social aspirations and biologic needs imposes certain limits on the diversity and reach of human motives and the sublimating endeavors chosen by self-determination.

Genetically, a chaotic lack of uniformity in human societies is prevented by various principles of selection, and by the fact that the cultural forces which mold, as well as the formative elements which secure moldability on the human level, are actually end-products of the same evolutionary process. Viewed in this light, they are like the two sides of a coin, defying analysis as independent variables [6, 16]. Hence, the inability to separate the two sets of determining factors can only in part be ascribed to the parental practice of raising one's own children. A reflection of this virtual inseparability is seen in the fact that most test devices for measuring meaningful personality differences have proven refractory to standardization [5, 13]. Only with increased accuracy in the measurement of normal trait variations will it be possible in genetic studies to realize the potentialities of psychometric methods of personality evaluation.

Apart from such unavoidable limitations on the assessment of gene-specific personality components, the twin study method represents a very useful procedure for appraising the effect of heredity on many behavior variations, both normal and abnormal. The technical efficacy of the method is matched by its economy and versatility as a sampling procedure, and extends to intricate population studies which call for a comparative analysis of individual adjustment and survival values. These advantages are most apparent in the investigation of traits requiring intra-family and longitudinal comparisons under controlled conditions, and personal contact with families from various population groups, including some whose private affairs might not otherwise be open to study. Procedurally, it is no real disadvantage that twins cannot be separated before they are born, or that they cannot be provided with two mothers of different age, personality, or health status.

The popular notion that the behavior patterns of one-egg twins resemble each other chiefly because of unusual similarity in their early environments has yet to be substantiated. Actually, if confirmed, the argument would strengthen rather than weaken any correctly formulated genetic theory. Psychodynamic concepts, too, are predicated on the premise that man is selective in regard to important aspects of his life

experience and takes pride in being responsible for his own formula of adjustment [1, 17].

In the area of normal personality variations, gene-specific derivations have been shown by comparative twin data to range from physical, coordinative, physiognomic and temperamental characteristics to intellectual abilities, affective regulations, and special talents [7, 9, 10, 18, 20]. In between are sex maturation patterns, variations in antibody production and neurohormonal alarm reactions, the capacity for longevity, and the ingredients for sustained tolerance of physiologic or psychologic stress, a highly essential prerequisite for a well-balanced personality [12]. It is well known that each individual has his own threshold of adaptability to different types of stress, and his own pattern of stress symptom formation.

Consistent similarity in the composition of these personality components is not found in the absence of genotypic similarity. Two-egg twins of the same sex tend to differ as much in their personalities as do any siblings reared together or apart. In one-egg twins, even pronounced differences in life experiences, however adverse, are rarely potent enough to erase basic similarities in appearance and general personality traits. The brief histories of a few typical twins may help to illustrate this point.

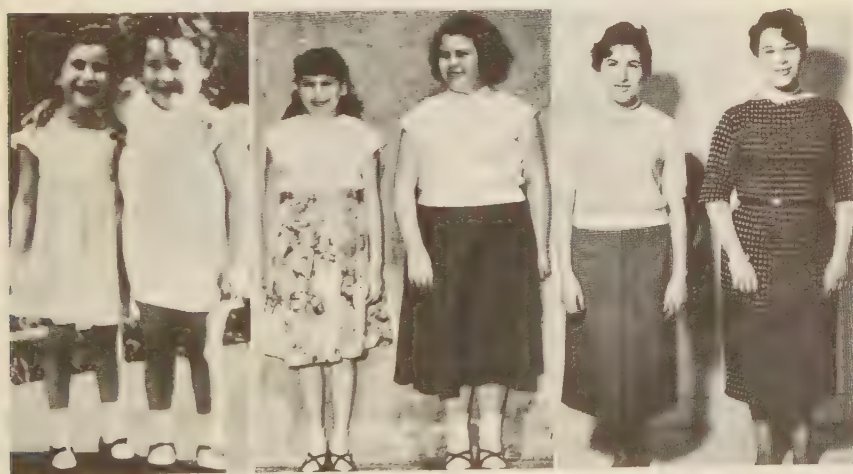


Fig. 1. Developmental differences in two-egg twins reared together.

The two-egg pair from an average middle-class home, shown in Fig. 1, falls within the normal range, despite striking dissimilarities in physical and mental development. Before puberty, the girls differed in height by

4 inches, in weight by 42 pounds, and in intelligence quotient by 22 points. The bright girl is no longer as thin as she used to be, nor as constricted in the emotional sphere. Possessed of strong intellectual strivings, she is doing well in an academic course, while her dull-normal, belligerent and emotionally immature twin sister has trouble with her commercial course.



Fig. 2. Similarities in one-egg twins reared together.

The one-egg twins in Fig. 2 come from the same locality and socio-economic background as the preceding pair. Both honor students now in college, they are still indistinguishable either by their appearance or any of their test performances. Except for minor fluctuations in their degrees of maturity and self-reliance, no real difference has emerged between their equally pleasant and well-balanced personalities.

The persistence of similar trends in the integrative and adjustive capacities of one-egg twins is illustrated by the 24-year-old college graduates shown in Fig. 3. Although one of them has been severely handi-



Fig. 3. Monozygotic twins discordant as to cerebral palsy.

capped by a spastic-paralytic form of cerebral palsy and will certainly never be a general, both young men have reached nearly the same level of superior intellectual ability and emotional equilibrium. In spite of considerable difficulty with speech, motor co-ordination, visual imagination and the handling of non-verbal material, the spastic twin is friendly, efficient in his office work, and gets along well with people. A notable difference between the twins is in their attitude toward religion, the spastic being the one who takes a very active interest in it.

Equally remarkable are the two girls in Fig. 4. Although they are one-egg twins whose parents are both deaf, early total deafness manifested itself in only one of the pair. Both girls are friendly, alert and well-behaved, and on the Vineland Social Maturity Scale achieve about the same level of performance. The deaf twin, before she reached the age of two, had a habit of tearing out her hair whenever she was angry. Gradually, however,



Fig. 4. Monozygotic twins discordant for deafness.

like her hearing twin she learned to vent her fury on the more impervious fur of her toy rabbit.

In another pair (Fig. 5 and 6), a different stress situation arose from body changes associated with isosexual precocity. The taller twin developed signs of early feminization before her sixth birthday and began to menstruate at the age of 6 $\frac{1}{2}$, followed six months later by the development of similar symptoms in the other twin. In the absence of any detectable organic lesion in the brain or ovaries (Dr. Grumbach), precocious puberty would here seem to be an extreme constitutional variation set off by hypothalamic influences.

The present difference in osseous development and sexual precocity (Fig. 6) is not matched by corresponding discrepancies in intellectual performance or emotional adjustment. Although the more matured twin seems to show less curiosity about the body, and a stronger identification



Fig. 5. One-egg twins partly concordant as to sexual precocity.

Height 48", weight 63 lbs.
Onset of precocious symptoms about 6.4 years
no menstruation (6.9 years)
less advanced osseous development
17-ketosteroids 2.3
average intelligence (I Q 95)
less mature and controlled;
tending to be aggressive
moderately jealous.



Height 50", weight 67 lbs.
advanced feminization since
5.8 years of age
menarche at 6.6 years
more estrogenized vag.
smear
17-ketosteroids 3.8
average intelligence (I Q 93)
normal behavior without
apparent anxiety
strong identification with
mother.

Fig. 6. Comparative data on one-egg twins with some difference in sexual precocity
(age 6½)

with the mother, neither girl is noticeably perturbed by an experience for which they were sufficiently prepared.

The adjustive disparity that developed in the sturdy twins shown in Figs. 7 and 8 was precipitated by a malignant schizophrenic psychosis in the wife of one of them. After years of struggling against the disintegration of his home and business interests, the luckless twin at the age of 53 became despondent and began to drink excessively. Incidental to these complications were over 60 electroshocks and bilateral breast operations necessitated by prolonged cortisone medication.

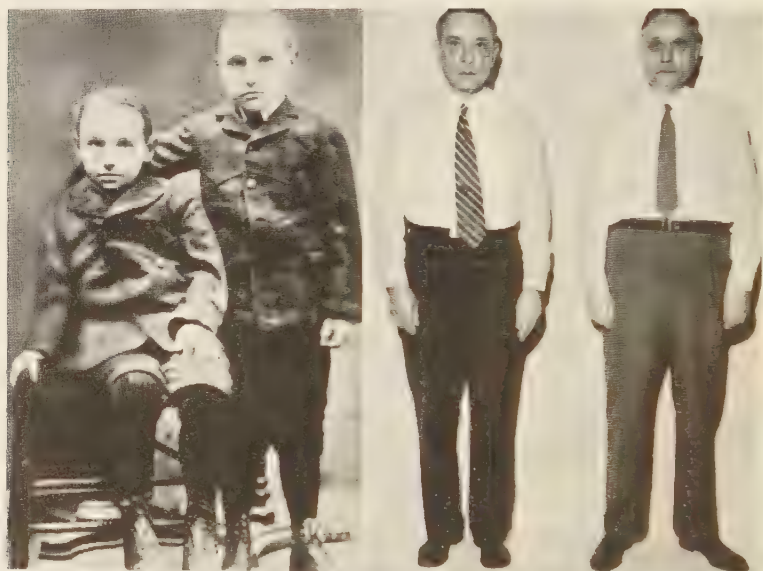


Fig. 7. The Z twins at the age of 8 and 60 years.

Residual corollaries might be seen in any of this twin's present symptoms, which include impoverished affectivity, impaired memory, extreme emotional dependence, poor stress tolerance, and a considerable loss of weight (Fig. 8). The only trouble is that the other twin, without a comparable history, shows nearly the same degree of impairment in memory and intellectual functions, gross tremor under stress, and even a slightly higher deterioration quotient. On the whole, the contrasting life situations of the twins have not obscured the remarkable similarities in their basic personality characteristics.

As to behavior disorders that are not sufficiently explained on a situational or experiential basis, the list of conditions for which complete twin

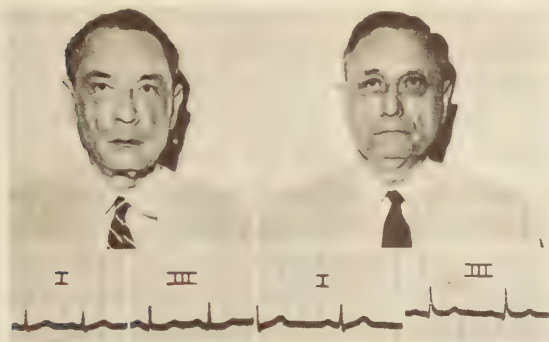


Fig. 8. Comparative data on one-egg twins discordant as to reactive depression and alcoholism.

Normal EKG; PR .14; QRS .06

Strained family life; overdedication to work; history of depression and recent alcoholism, impoverished affectivity.

Weight 165; B. P. 105/75; pulse 96

Total cholest. 294; sugar 111;

urea-N 13.8 mg%

normal EEG; fine tremor

average intelligence; I Q 108

moderate impairment in memory, learning and arith. abilities (D Q 40%)

marked dependence, poor stress tolerance.

Similar EKG; PR .16; QRS .06

Comfortable home; prosperous business partnership with twin; noticeable decline in vigor and acuity.

Weight 196; B. P. 115/75; pulse 78

Blood cholest. 213; sugar 116;

urea-N 9.5 mg%

normal EEG, gross tremor under stress

average intelligence; I Q 109

impaired memory and simple

assoc. learning rate (D Q 43%)

moderate anxiety with fair emotional control.

sibship data are now available is headed by the schizophrenic and manic-depressive types of psychosis. Since these two disorders do not occur interchangeably in the same twin pairs, they are assumed to be genotypically specific. The potentialities for a cyclic psychosis are probably associated with a subtle disturbance in a neurohormonal control mechanism which ordinarily protects a person from having harmful extremes of emotional responses.

While the tendency to exceed the normal range of mood alterations apparently requires the mutative effect of a single dominant gene with incomplete penetrance, the metabolic deficiency in a potentially schizophrenic person is most likely the result of a recessive gene.

Involutional melancholia and other non-periodic forms of depressive behavior in the involutional and senile periods have been shown by twin family data to be unrelated to the manic-depressive group of disorders.

There is an indirect link with the schizophrenic genotype through certain forms of emotional instability characteristic of schizoid personality traits. Other symptoms of maladjustment in the senescent period may arise either from gene-specific metabolic dysfunctions peculiar to the senium, or from graded differences in general health and survival values.

Homosexual behavior in the adult male continues to yield a higher one-egg concordance rate than any of the other conditions investigated. This finding points to a disarrangement in the balance between male and female maturation patterns, resulting in a shift toward an alternative minus variant in the integrative process of psychosexual maturation.

In regard to all these disorders, twin family studies are helping materially to focus attention on persisting obscurities in their etiology. Generally, the objective of genetic investigations in man is not only to demonstrate that gene-controlled phenomena play a role in the differentiation of normal and abnormal behavior patterns, but to determine how this action takes place.

In conclusion, it may be said with some measure of satisfaction that recent progress in the psychogenetic area of personality organization has been encouraging. An immediate result has been the improvement of our knowledge regarding the interacting bipolarity of human life. Growing insight into this interaction will gradually unfold a better understanding of variable behavior patterns in terms of physiochemical processes powered by genic elements.

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CHANGING INTELLECTUAL FUNCTIONS IN SENESCENT TWINS *

By *L. F. JARVIK, F. J. KALLMANN, A. FALEK*
 and *M. M. KLABER*

Available research data on the nature and extent of changes in intellectual functions brought about by aging are contradictory. It is, therefore, not surprising that the potential effect of genetically determined variations in this area has been so little explored.

* Presented at the First International Congress of Human Genetics (Copenhagen, August 1-6, 1956), as the ninth consecutive report on the progress of a study, which has been supported by grants from the Rockefeller Foundation (1945-1951) and the Division of Research Grants of the National Institutes of Health (1952-1956).

According to cross-sectional studies [4, 7, 15, 18], psychometric scores show a consistent decline with advancing age. Beginning shortly before or during the fourth decade of life, this trend is supposed to be more pronounced in performance than in verbal tests [2, 6, 14]. However, in the presenescent period no equivalent decrease has been found in longitudinal investigations concerned with changes in intellectual abilities during the later years of adulthood [1, 12, 17]. On the contrary, two of the three surveys conducted produced evidence for an increase rather than a decrease in test scores.

In order to shed some light on this important question, a psychometric twin study was organized in 1947 in connection with the collection of a New York State sample of twins over age 60 [8, 9]. The 300 test cases, which were chosen from a series of over 2000 senescent twins, had to meet the following requirements:

1. The two members of a pair had to be of the same sex and testable. The health criteria included normal intelligence as well as the absence of physical or mental illness.

2. Both twin partners had to live at home (outside of institutions) and reside within the area covered by other units of our research organization.

Incidental factors reduced the size of the original test group from 150 to 127 pairs. Of this total sample, 62 pairs were retested with the same battery after a period of approximately one year (mean interval 11.7 months). Another series of retests was administered in 1955, after a period of almost eight years (mean interval 7.8 years). At that time, our sample of testable twins had dwindled to 36 complete pairs and 7 single survivors.

The results of the first two test rounds, reported a few years ago [5, 8, 10], revealed that the mean intra-pair differences in test scores measuring various intellectual abilities were consistently smaller in one-egg than in two-egg pairs. With the significance of genetic variations having been previously established in regard to intellectual capacities in childhood and adolescence [3, 16, 19], our study of senescent twins confirmed the persistence of gene-specific differences of this kind during adult life. The purpose of the present report is to investigate more specifically the extent of intellectual changes taking place in the period of senescence, as well as the part played by genetic factors in differentiating such changes.

The essential specifications regarding the size and composition of our present series of test cases are summarized in table 1. The sample consists of 47 females (21 pairs in addition to 5 single survivors) and 32 males (15 pairs plus 2 single survivors). Of the 36 complete pairs, 26 are monozygotic (72.2 %) and 10 (27.8 %) dizygotic.

Table 1. Test series of senescent same-sexed twin pairs

	Monozygotic		Dizygotic	
	1947	1955	1947	1955
Male	34	11	19	4
Female	41	15	26	6
Total	75	26	45	10

The preponderance of female twins in this age group is in line with statistical expectation. The same is true for the observed disproportion between one-egg and two-egg pairs. The increase in the expected proportion of one-egg pairs is explained at least in part by the relatively small differences in their intra-pair life spans [11, 13].

The distribution of subgroups formed by sex and zygosity approximates that found in the original sample of 127 pairs, where the largest group was that of monozygotic females (34.2%). This group was followed in order by monozygotic males (28.3%), dizygotic females (21.7%), and dizygotic males (15.8%). In about one-half of these pairs, retests were precluded by the death of one or both twin partners.

The present age range of the survivors is from 68 to 87 years, with a mean age of 74.5 years at the time of the retest in 1955. As in our first report [5], the test population may be described as a literate, white, native-born, non-institutional sample. All important details concerning residence, education and occupation of the test cases have been previously reported.

Table 2. Longitudinal data on intellectual decline in senescence

Test	Number of Index Cases		Mean Test Scores of Total Sample (1947)	Mean Test Scores of Retested Subsample		
	Total Sample	Sub-Sample		1947	1955	Decline in %
Vocabulary	240	72	28.40	30.74	29.82	3.0
Digit symbol	190	67	27.81	29.31	25.75	12.1
Block design	206	66	13.39	15.09	12.65	16.2
Similarities	230	78	8.85	10.35	9.68	6.5
Tapping	240	75	66.10	72.61	56.92	21.6
Digit Span	239	74	9.98	10.28	9.88	3.9

The psychometric battery (table 2) consisted of the following six tests:

- (a) List I of the Stanford-Binet (*Terman* [1916]) vocabulary test—the best single indicator of “general intelligence”, and particularly suited for a group of aged people.
- (b) Three measures of visual-motor co-ordination: pencil tapping, block design, and digit symbol test.
- (c) Digit span test, useful as an indicator of rote memory.
- (d) Similarities test for assessing the faculty of abstract reasoning.

Except for the pencil tapping and vocabulary tests, the entire battery was taken from the Wechsler-Bellevue Intelligence Test, Scale I.

Because of physical infirmities associated with aging, especially impaired vision or hearing, all six subtests could not be administered to every subject. Though minor in its overall effect, this discrepancy made it advisable to tabulate separately the actual number of individuals for each subtest.

The total retest data obtained in 1955 have been arranged in such a way that the mean raw scores of the subsample of 79 survivors can be compared not only with their own previous scores on the same tests, but also with the mean scores of the original test group of 240 twins. The previous test scores used for this comparison are either those obtained in the first test round (1947–1948) or, where possible, the first retest scores (1948–1949). In order to equalize the effect of familiarity with testing procedures upon the results of retests given eight years later, either set of data has been used and will be referred to as the “original score”. Since the first test-retest reliability coefficients for the subtests varied only from 0.903 to 0.996, it may be assumed that the given scores represent not only a reliable estimate of performance, but also a well-standardized basis for the subsequent series of retests.

It is shown by the data in table 2 that compared with the original test results, the mean retest scores for the same subjects are lower on all tests. The decline is less pronounced on verbal than on performance tests and is statistically significant ($p < 0.01$) only for the latter group of tests (digit symbol, block design, tapping).

If the raw scores of the four subtests taken from the Wechsler-Bellevue battery are transformed into scaled scores according to *Wechsler's* specifications [18], the mean scores of the retest series are found to be consistently higher than those of the standardization group. In agreement with the findings of *Doppelt* and *Wallace* [4], there is no evidence for a significant difference between the sexes.

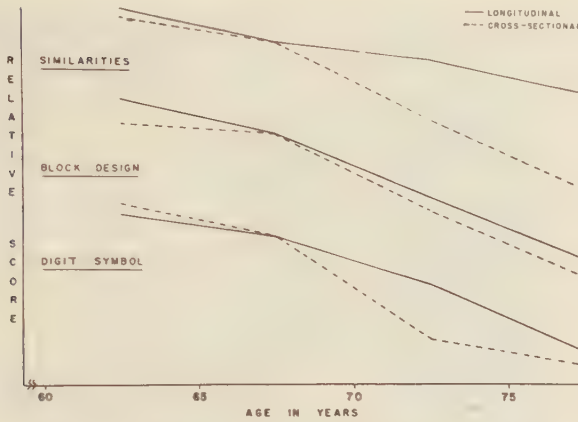


Fig. 1. Trends of intellectual decline in senescence (longitudinal and cross-sectional test data).

Despite similar trends toward scores decreasing with advancing age, it is demonstrated by our graphically arranged data in fig. 1 that the rate of decline in our sample during the observed interval of eight years has been smaller than that inferred from cross-sectional studies [4]. Moreover, although the mean scores of our sample declined on the whole, there are considerable variations from one individual to another. While most subjects show a decreasing score, on retest some have either the same or a higher score.

Another interesting finding is that compared with the original total test population, the retest series of survivors achieved higher mean scores on all original tests. It may be that these differences reflect a measurable degree of selectivity with respect to biological survival values. However, the given differences are below the level of statistical significance and need verification to substantiate this hypothesis.

Conversely, it could be postulated that lowness of original scores reflected the subsequent inability to survive the eight-year interval between test and retest. To investigate this possibility, we have rearranged our data in such a way that the mean scores of the 69 twin subjects who died before the retest can be compared with those of a group of survivors of comparable age. Once again, the results of this comparison show no statistically significant differences. However, until such time as further data on this point are available, one cannot disregard entirely the fact that on four tests the mean scores of the deceased group are lower than those of the survivors.

In view of the specific interests of this Congress, it is noteworthy that the test population used in this longitudinal study consists of both one-egg and two-egg twin pairs of the same sex. Genetically, it is important to demonstrate again and again that one-egg twin partners maintain their basic similarities throughout life, while two-egg twins tend to remain dissimilar until a well advanced age. In other words, genetic personality factors continue to express themselves even in the period of senescence.

The similarities persisting in one-egg twins of either sex are illustrated by the two pairs in fig. 2. In contrast, the dissimilarities in aging two-egg twins (fig. 3) are striking. The second photograph of each pair was taken when the twins were retested in 1955.



Fig. 2. Similarities in one-egg twins.

As to mean intra-pair differences in test scores (fig. 4), it will be noted that the intra-pair differences in the two-egg group are consistently greater than those found in the one-egg group. In the original sample, the difference



Fig. 3. Dissimilarities in two-egg twins.

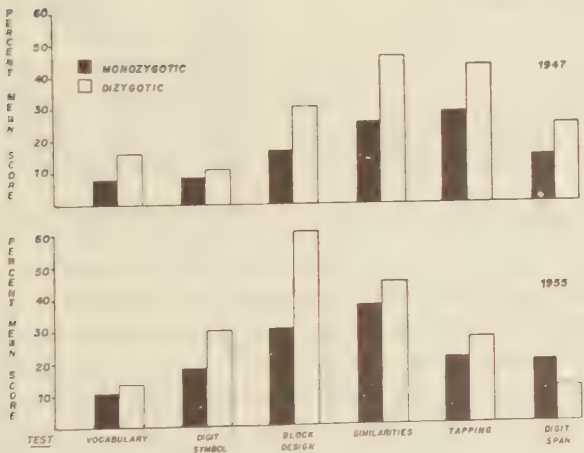


Fig. 4. Comparative mean intra-pair differences in test scores (1947 and 1955).

between the two zygosity groups was significant at the 0.01 level of confidence for the vocabulary, digit symbol, block design and tapping tests. In the retest series, which is numerically too small to show statistically

significant differences between the zygosity groups, it is still apparent in five of the six tests that the mean intrapair differences are greater in two-egg than in one-egg pairs. The data obtained with the digit span test constitute the only exception to this trend.

With respect to changes in the size of intra-pair differences during the interval between test and retest (fig. 5), one-egg twins show an increase in mean intra-pair differences which is quite consistent though relatively small and statistically not significant. However, since the same trend is seen on all six tests for a series of 26 pairs, the given increase may represent the effect of various incidental concomitants of the senium. Such conditions are apt to interfere with the expression of basic similarities in general aging potentials.

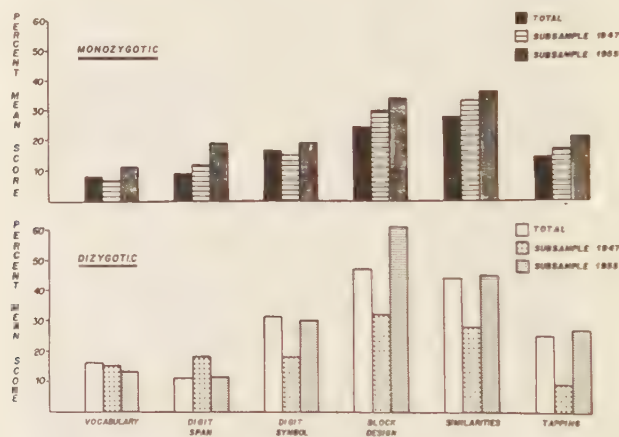


Fig. 5. Variations in mean intra-pair test differences.

In the two-egg series which has now been reduced to ten pairs, the intra-pair differences in retested pairs are of the same magnitude as those in the entire original sample of two-egg twins. However, if the comparison is limited to pairs who were testable after eight years, the mean intra-pair differences in retest scores tend to be larger than those in the original scores. It may be hypothesized, therefore, that two-egg twins, if they are to be expected to remain available together for retesting eight years later, have to be selected on the basis of greater than average similarity in test performance.

On the other hand, if the retest scores of surviving two-egg pairs are compared with the original scores of pairs with one subsequently deceased

member, the intra-pair differences in the latter subsample are found to be greater on four tests. Here again, it may be surmised that in the surviving series there has been a selection in favor of the genetically most similar two-egg pairs.

In conclusion, the methodological difficulties inherent in a longitudinal study of aging twins should be mentioned. It will be recalled that an overall sample of more than 2000 twin subjects over age 60 yielded only 127 testable same-sex pairs for the original psychometric series, and no more than 36 pairs for retesting after an interval of eight years. In regard to intra-pair differences of a low order of magnitude, a surviving sample of complete pairs may be expected to produce no more than general trends.

As to the mean test scores for the 79 individuals, however, our data show a consistent but limited decrement in intellectual abilities. By and large, this finding is in agreement with the trend observed in cross-sectional studies, but the slope of the decline in our longitudinal investigation is less than that expected on the basis of survey data.

Another interesting observation is that the retested twin pairs scored higher on the original tests than did the total sample tested previously. It is possible, therefore, that a relationship exists between test score level and survival potential. The implications of this hypothesis are inconclusive without corroboration by data from larger samples. The same reservation holds for the finding that two-egg twin partners most similar in test scores in the senescent period seem to have the best chance of surviving together.

Genetically, it is of particular importance that the mean intra-pair differences in the test scores of two-egg twins are consistently greater than those of one-egg pairs, both on the original tests and on the retests. Our conclusion is, therefore, that the part played by genetic factors in producing measurable variations in intellectual functions and their decline remains clearly demonstrable during the period of senescence.

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UNIOVULAR TWINS BROUGHT UP APART

(*Preliminary Report of a Psychiatric-Psychological Study*)

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The first investigation of uniovular twins brought up apart was carried out by Popenoe in 1922. The same twins were re-examined by Muller in 1925, and by Saudek in 1933.

In 1937, Newman, Freeman and Holzinger published their book "Twins: A Study of Heredity and Environment". They here reported their research on 19 uniovular pairs of twins who had been reared apart. Newman and Gardner added yet another pair to this group in 1940.

In 1942, Barbara S. Burks gave a detailed description of her investigation of a single pair of separated twins, but, unfortunately, she died while work was still in progress. The results obtained up to her death were published by Anne Roe in 1949. In the latter paper an additional 4 pairs are mentioned. However, one of these pairs, as is apparent from the article in question was probably binovular.

The concordant appearance of psychotic states in twins reared apart has been described by *Kallmann* in 1938 and by *Slater* and *Craige* in 1945.

Apart from the above-mentioned cases, the literature only provides isolated case reports on uniovular twins, and the main part of these reports refer to twins that have not presented any special mental illness.

The total number of reports published concerning uniovular, separated pairs of twins probably does not exceed 35 cases, but in recent years investigations of such persons have been recommenced in several different countries.

The most extensive investigation of separately reared twins undertaken hitherto is at present in progress in Great Britain, and is being carried out by *James Shields* of the Institute of Psychiatry, Maudsley Hospital, London. Mr. *Shields* submitted a paper to this congress on his research; he is unfortunately unable to be present. Similar investigations have been commenced in Stockholm, Sweden.

The present Danish investigation commenced in 1954 at the Psychiatric Institute, Risskov, Aarhus. We there had the opportunity of studying two pairs of uniovular twins grown up apart. In co-operation with the Institute for Human Genetics in Copenhagen, at which the investigations are continuing, we began the collection of separated twins resident in Denmark. We have profited considerably in this respect from the registration of Danish twins born between 1870 and 1910 which is being carried out by *Hauge* and *Harvald*. We have included all the twins, whether they have shown signs of mental abnormality or not, demanding only they (1) were separated during their entire childhood and (2) were uniovular. The binovular pairs we have encountered have not been subjected to special examination.

Our material at present comprises 8 pairs of uniovular twins. A 9th pair was included in the investigation recently, and we have reason to believe that several further pairs will be found in this country. The 8 pairs examined comprise 6 female and 2 male pairs, the ages varying from 22 to 72 years.

The separation of the twins has in all instances taken place during early childhood. In 6 cases the separation occurred before the end of their first year of life, in 1 case as early as the day after birth. In 1 case the twins were reunited during the latter part of their childhood, parting again later. In the other cases, the twins first met each other when adults, in 2 cases as late as in the 35th and 40th year. In 3 cases the partners grew up without knowledge of each other, and were first brought together by common acquaintances after they had been repeatedly mistaken for each other. In 2 of these 3 cases, where the separation had been complete, we were able

to examine them in direct connection with their reunion. All the twins concerned have continued to live separate from their partners, and although there has been a certain amount of interaction between partners in some instances, it has been slight.

With reference to the *environments* in which the twins have grown up, the partners of each pair have been reared under conditions that differed more than they resembled each other regarding social-economic and cultural factors when one takes into consideration the relatively uniform structure of the Danish society. The twins' schooling and professional or trade training, as well as their lives as a whole have in most cases been different. Finally, we want to stress that regarding the childhood environments, there have been differences throughout the whole period in respect of family structure, the twins' relationships to their parents, the relationship between mother and child and whether the twin was an only child or had siblings, etc. In this respect, the material presents nearly all possible variations of environmental constellations.

The examinations which are carried out partly by means of *psychiatric interviews*, and partly by *psychological testing*, have been planned as a long-term project. We have had as our aim that of investigating each pair of twins as intensively and over as long a period as possible. This has been practicable because the twins have proved themselves to be very co-operative, and because geographical conditions have made it possible for the twins to come to frequent examinations in Aarhus or Copenhagen. It has been possible to keep in contact with the twins ever since they were first approached in this matter, and repeated visits have been made to their homes and relatives as far as this has been feasible. A considerable amount of information elucidating the twin's families has been collected from hospital case-histories, the archives of the Copenhagen Institute for Human Genetics, a number of social institutions and other sources.

The *psychological testing* is based on a number of tests in general clinical use in Denmark, supplemented with some other, more special tests. All twin pairs have been examined with the *Wechsler-Bellerue intelligence scale* (Adult I) in translated form, *Raven's progressive matrices* (1938), the *Rorschach* test and *Rapaport's association test*. In addition, most pairs have been examined with *Lüscher's* colour selection test, *Szondi's* picture test and a few others, and the twins have also completed a personological questionnaire. Retesting has been commenced with Wechsler's, Rorschach's and Lüscher's test. The retest intervals will be somewhat different in length, but will in all cases exceed 6 months.

The examinations are carried out by a psychiatrist and a psychologist

who work independently, among other things because of practical reasons. Parts of the material are registered by means of a wire-recorder. It is naturally the aim to formulate independent descriptions of the twins' personalities, and secondarily to co-ordinate the data obtained, but as the examinations are as yet incomplete, we have not commenced to collate the material.

Apart from the usual medical examination and anthropometric measurements, other special examinations include ophthalmological, electrocardiographic and electroencephalographic investigations.

With material of this extent, it is naturally more than usually important that the *ovularity diagnosis* rests on as firm a basis as possible. The *blood types* have been determined, including a total of 8 blood-type systems and their corresponding sub-groups, and *finger-hand-print* examinations have also been carried out in all cases. Sufficiently reliable information regarding the *afterbirth* has only been available in two instances; in both the twins were dichoriatic.

We are unable in this paper to present the results of the work carried out hitherto. The documentation of even single postulates would demand the detailed report of case-histories and test results.

The object of this report has been to sketch the plan of our investigation and the procedures we have employed. We hope in this manner to contact all who either are in the process of carrying out similar research or who are interested in taking it up. Although investigations of separated twins offer research workers considerable advantages, they also have their special difficulties and problems. The most important problem is perhaps the fact that it is unlikely that any country can collect a large number of uniovular twins who have been reared apart. Taken together, the investigations at present proceeding independently will presumably increase the number of investigated twins up to about a hundred uniovular pairs. If the results of these various investigations are to be compared once they are available, it is certainly necessary that as many of the investigations as possible are planned in co-ordination or adjusted to each other as early and far as possible. It is our opinion that such coordination of research will make it possible to reach more general and univocal conclusions than previous investigations of separated uniovular twins have been able to produce.

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A TWIN STUDY IN MILD ORGANIC DETERIORATION

By S. J. DENCKER

The purpose of this study was to make a systematic clinical follow-up of a group of twins with closed head injuries, using same-sexed co-twins as controls.

The material has been systematically collected from all the surgical clinics in Scania, a county in the south of Sweden. It is non-selected and includes in-patients admitted under the diagnosis of concussion of the brain. The primary material consists of 14,647 patients. The twins in this study have been collected from a complete index of twins born in Scania since 1880. The material includes 167 same-sexed pairs. In 121 cases both partners were alive at the time of the proband trauma. Of these, 81 pairs are dizygotic and 40 monozygotic which gives an incidence of uniovularity of 36 %.

The twin diagnoses were based on an anthroposcopic scheme, including finger print and extensive blood group determinations.

In this preliminary report only the uniovular pairs have been considered. In 4 of these pairs one or both members have died and will not be used in this analysis. In one case both committed suicide, in another case the co-twin. In the other two cases the probands died from somatic diseases.

All the monozygotic pairs between 10 and 60 years—i.e. 32 pairs—have been subjected to a detailed psychiatric, neurologic and psychometric investigation except one case which refused to be tested.

In all cases more than 2 years have elapsed since the trauma. The choice of tests was based on the results from a pilot study of some 15 cases with a classical post-traumatic syndrome. The tests included an intelligence test (Raven's progressive matrices); a few tests of concentration and immediate memory; tests of verbal fluency, speed of tapping and simple reaction time;

the mirror test; a modified version of the Goldstein colour form sorting test; Ward Halstead's tactual performance test; a test of visual perception (after *Strauss and Lehtinen*) and a visual-motor test of speed and attention ("distributator").

Each twin member was interviewed 3-5 times, additional information was obtained from their relatives. The neurologic investigation included physical examination (these results are without interest in this connection); flicker fusion test and electroencephalographic examination. No significant findings were recorded with these two methods, not even in cases with severe injuries.

The following tests proved to discriminate between the brain-injured and the control groups at the 2-5 % level of significance, viz: the Goldstein colour form sorting test, the visual perception test, the mirror test and the distributator. The number of tests which discriminated between the groups is beyond the level of chance expectation. Classification of the material with regard to birth-order, birth-weight, handedness and dominance gave no significant differences between the groups.

The results of these tests which are mainly associated with cognitive functions suggest that deficits shown by the brain-injured group in comparison with their controls, consist of a reduced ability for abstraction (as defined by *Goldstein* and others); a reduced speed of perception and some difficulties in adaptation to an altered or unusual task (as measured by the mirror test). It should be noted, however, that the intelligence test did not discriminate. Nor did tests of concentration, fatigability, and memory, which is interesting as such symptoms are usually reported in the post-traumatic syndrome.

Another finding in the psychiatric field was that the probands generally were more torpid ($0.01 > P > 0.001$) and rigid ($P < 0.001$) than their co-twins. In 5 cases they were also more viscous or sticky. On the other hand, there was no difference between the groups with regard to their capacity for work, the presence of psychiatric illness or neurasthenic traits. But I was able to find a significant relationship between these symptoms and the factor of dominance.

As this factor generally can be studied in this twin material and it seems to be of a non-traumatic environmental quality its character will briefly be discussed.

From early childhood onwards, one of the twins is generally the leader, the organizer and the one, who is responsible for the contacts with the environment. His partner is generally submissive to him in this and many other respects. Only in two out of the 40 pairs did the leadership change.

Classification of the material with regard to this factor of dominance shows significant differences between the groups in the following respects: in the submissive group there was a significantly higher frequency of psychiatric illness in the broad sense (13 cases versus 1), neurasthenic traits ($P < 0.01$) and neurotic traits (here defined as tendency to tenseness, passivity, dependency and inhibition ($P < 0.01-0.001$)). Dysphoria was more frequent in the dominant group ($P < 0.001$). This agrees with the findings of *Schulte* and *Slater* who found the more dominant partner to be more spared by schizophrenic process.

As *Shields* I find a significant relationship ($P < 0.001$) between higher birth-weight and being the more dominant partner. There was also a significant tendency for the member with higher birth-weight to be the heavier one even in the future ($0.05 > P > 0.01$).

From the etiological point of view one question is of great importance: can this relationship be related to environmental factors or not? Considered as groups there was no difference between the dominant and the submissive members in any of the cognitive tests, the number of probands being the same in the two groups. This excludes the possibility that the dominance is associated with a testable organic defect. Anamnestic data such as school results, somatic diseases and physical frailty did not discriminate between the groups either.

These findings seem to suggest that the factor of dominance has no pathological organic correlates in the central nervous system. It is more probable that the relationship is due to chance, the heavier member being more likely to become the dominant one. Etiologically this relationship can then be considered as an environmental factor, possibly of psychological character, which has no relation to the closed head injury.

If the material is classified according to both trauma and dominance I found significantly more neurasthenic persons among the submissive probands. This favours the belief that the closed head injury per se was of less importance for the development and persistence of neurasthenic traits than other environmental factors. Even in those 4 cases where the dominant proband was the more neurasthenic member, this tendency was present prior to the trauma in 3 cases.

Also in regard to the more subjective post-traumatic symptoms of chronic type such as headache, dizziness, impaired memory, etc., the trauma in this material appears to be of negligible significance, when compared with other factors, in this case genetic factors. This is because these symptoms are as frequent among the traumatic twins as among their mono-

zygotic co-twins. While in the binovular material there was a significant difference between the groups in this respect.

The results can be *summarized* as follows: As regards chronic subjective post-traumatic symptoms as headache, dizziness, etc., there are indications that genetic factors may be of greater importance than the actual head injury. Objective findings, such as psychiatric illness, neurasthenic traits or reduced capacity for work, are found with equal frequency in the brain-injured and the control groups. These symptoms are due rather to environmental factors, independent of the trauma. On the other hand, the psychometric investigation shows some organic deficits in cognitive functions in the closed head injury group as compared with the monozygotic control group.

It should be stressed that in no case was this organic deficit after closed head injury striking. On the contrary, the symptoms were so subtle that they could not have been proved without using monozygotic twins as controls.

Kaij, L.: *Acta genet.* 7, 437-441, 1957

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DRINKING HABITS IN TWINS

By L. KAIJ

This is a preliminary report of an investigation of 174 pairs of twins registered between 1939 and 1953 as alcohol abusers in the public registers in South Sweden.

The material consists of 23,221 men registered on account of alcohol abuse ranging from a single conviction for drunkenness to severe chronic alcoholism. Among these, the twins were picked out by the aid of a complete register existing at the Psychiatric Dept. in Lund and containing all twins born in the province since 1880. This method of selection guarantees the series to be consecutive. Only same-sexed male pairs were considered. There were in all 310 probands, which is $1,33 \pm 0,08$ % of the total primary material. 3 probands had by mistake come into the material and 11 ap-

peared twice. When these 14 were excluded together with those probands, whose partners had died young, there remained 215 to be investigated. They belonged to 174 pairs, which means that in 41 pairs both members were probands.

Of the 348 persons 296 were examined by the author personally. Of the remaining, 21 are dead, 3 have emigrated, 7 were untracable and 21 are sailors or live too far away. Of 7 pairs neither twin has been examined, and in 3 of these pairs no information is available except the official. The mean age of the material is 39.7 years.

The study was performed as a field investigation and all twins were visited in their homes. They were therefore seen in their environment and their relatives were more readily accessible, but an intimate conversation was not always possible. Histories were taken up by informal conversation. A questionnaire provided a certain guarantee for standardisation. It served as a guide but was no master. Questions about alcohol were postponed until the end of the interview. As this part was one of the most important, no pains were spared to get as good a personal contact as possible before the subject was brought up. It is easily understood that the topic was not always so very popular. Immediately after the interview a psychiatric status and a general estimate of drinking habits were taken down. The MZ pairs were later examined with psychological tests at the Psychiatric Dept. As far as possible information about the twins was collected from their relatives or other persons who knew them.

The diagnoses of monozygosity were based upon the principle of polysymptomatic conformity. The ABO, MNS, Rh and Lewis blood groups were determined. 67 probands were members of pairs diagnosed as MZ, i.e. 32.2 %, which figure is hardly below the expected ratio of MZ among like-sexed pairs.

This report is only concerned with the drinking habits of the twins. As mentioned earlier there are considerable difficulties in estimating such habits. No standards exist, so what is moderate drinking to one person is excess to another. It is also wellknown that alcoholics often lose insight in their situation and have a tendency to deny or belittle their abuse. Many persons regard a serious discussion about their alcohol habits as improper or insulting and much maturity and independance is demanded from a person to be objective in this respect. Accordingly some persons were obviously conventional in their answers, some did not answer at all while others were surprisingly candid. It should be remembered that the persons in my material were not admitted to a hospital, but were visited in their homes apparently of no cause at all by an inquisitive doctor.

Their relatives are as a source of information on the whole more objective, but may occasionally be either protecting and understating or aggressive and exaggerating. As to the official registers, these have hardly any emotional errors and when the Temperance Boards intervenes a thorough investigation generally follows. However, far from all alcoholics are known to the authorities and advanced alcoholism may hide behind a single conviction for drunkenness. Still another source of information has been available by the Swedish legislation of "intoxicating liquors", which was only recently repealed. According to this law every purchase of wine and spirits was registered on a personal card. As there was a maximal amount (3 l. of spirits) per month per person, the purchases could not be graded by the total amount bought, but by the mode of buying e.g. regular or irregular purchases, purchases on several consecutive days and so on. As a final source of information there is the investigator's estimate at the interview. All examinations have been performed by myself, which means one frame of reference only.

To come to a final conclusion about a person's drinking habits, the different estimates have been compiled to form a final diagnosis. Even this must be subjective, as one must attach varying importance to different person's judgements, but as a rule the different statements were in accordance. The classification of drinking habits are shown in table 1.

Table 1. Classification of drinking habits

0	abstainers or below-average consumers
1	average consumers
2	week-end drinkers; above average
3	addicts and heavy abusers
4	chronic alcoholics

The groups have been defined with as great an accuracy as possible but space does not permit an account of the criteria.

In table 2 the twin pairs are plotted according to their drinking habits thus grouped, with the probands along the abscissa and their partners along the ordinate. Along the central diagonal of the square, one finds the concordant pairs, along the diagonals next to the central one, the least discordant and so on. To find out whether there exists any difference between MZ and DZ, the pairs along each diagonal are added together to form 5 classes of increasing discordance. It is necessary to proceed in this way when studying a continued and not alternative variable. In this way table 3 is obtained. In order to perform a χ^2 analysis, the two highest classes are here combined.

Table 2. See text. The question-marks indicate persons not examined and whose drinking habits could not be estimated

DZ						MZ					
?						?					
1						2					
2						1					
1						1					
6											

deterioration and dementia. To complete this study the MZ pairs have been examined thoroughly with a battery of psychological tests intended to cover different aspects of the personality and its deterioration. There are four possible patterns. The first is when one twin is alcoholic and becomes demented, while his partner is sober and intact. The second is when only one is alcoholic but both become demented. Such a pair has been published by *Slater* in his extensive twin study. The third possibility is that one twin is alcoholic and both remain intact and finally the fourth, when both are alcoholic but only one becomes demented. This part is perhaps the most interesting for it partly extends the use of a twin material beyond the boundaries of genetics and it may possibly contribute to the knowledge of organic mental deterioration.

Martensen-Larsen, O.: Acta genet. 7, 441-444, 1957

Copenhagen, Denmark

THE FAMILY CONSTELLATION ANALYSIS AND ALCOHOLISM

By O. MARTENSEN-LARSEN

Alcoholism is found much more frequently in some families than in others. The object of this study was to investigate whether a systematic family constellation analysis of alcoholics' families could reveal any factor in the family set-up, which could possibly be said to favour the rise of alcoholism.

In 518 alcoholic men:

50 were only child.

99 had no brothers (but one or more sisters).

139 were lastborn (about 25 % more than should sociologically be expected).

The surrounding sibs were just as often brothers as sisters. 10 were twins.

179 were "pseudo-twins", being preceded and/or succeeded by a sib within less than 18 months. Preceded were 80, succeeded 52. The pseudo-twin-partners more often were boys than girls.

Before the age of 15, 35 had lost both parents, 22 mother, 56 father.

In 463 wives:

38 were only child, 130 oldest child, 91 youngest child.

Their loss of parents ratio was (both parents/mother/father) 21-12-30. 112 were older than their husbands (twice the expected number). Thus in his choice of a partner the male alcoholic seems to seek "upwards"—in respect of the birth rank and the age of his wife.

In 524 mothers:

41 were only child, 167 oldest child and 73 youngest child. 204 were oldest sister, 88 youngest sister.

About 18% were older than their husbands. The succeeding sib ratio was 177 boys/220 sisters.

In 502 fathers:

only 23 were only child and only 45 had no brothers (but sisters). 145 were oldest child, 103 youngest child. 165 were oldest boy, 127 youngest boy. Preceding sib ratio: 191/134, succeeding sib ratio 214/152, brothers thus clearly prevailing.

Common findings in the fathers and mothers were their being most often from the upper part of the sibship, but this quality was seen much more pronouncedly in the mothers than in the fathers.

In 71 maternal grandmothers:

only one was only child. Oldest child were 31, youngest only one. 35 were oldest sister, 9 youngest sister. Preceding and succeeding sib ratios were in some favour of boys (24/15 and 37/29).

In 62 maternal grandfathers:

5 were only child, 30 oldest child and 7 youngest child. 34 were oldest brother, 10 an in-between brother and 9 youngest brother. In the sibs 98 brothers and only 71 sisters were registered. 16 had older wives.

Only recently we started investigations on paternal grandparents, one figure however deserves mentioning:

In 28 paternal grandmothers 12 were oldest child, while only 2 were last child. The corresponding figures in 34 paternal grandfathers: 10-8.

In all these figures those connected with the alcoholic men's maternal grandparents are the most outstanding. 13 couples showed both partners being the oldest sib of their own sex in their own sibship, compared to none, where they were both the youngest. If we divide the sibships in approximate thirds, we find 21 couples, where both partners belong to the upper third, while we find none where both belong to the lower third.

As these grandparents have rarely been in much contact with their future alcoholic grandchildren, we may imagine that they in their marriage develop a particular atmosphere, which in their daughters, particularly the oldest ones, produces some psychological qualities which, if they become mothers, risk to influence their boys in a way which provides them with the psychological set-up, which may predispose them to alcoholism. A thorough psychological interpretation is here needed. The finding of the "pathogenic" grand-parents however explains why alcoholism is often found in sibs as well as in cousins, leaving no reason to believe in a genetic pathogenesis.

141 alcoholic women:

were also investigated. 15 were only child, the rest mainly from the upper and lower end of their sibships and similarly mainly being the oldest or youngest girl.

Preceding sib ratio was 31/51, succeeding sib ratio 41/53—the sisters thus clearly prevailing.

The loss of parents ratio was quite remarkable: 10-0-38, showing that we found no alcoholic woman who had lost her real mother but kept her real father, while 38 had lost their father but kept mother.

In 125 mothers:

13 were only child and the rest rather evenly distributed throughout the sibship.

Preceding sib ratio was 31/49, succeeding sib ratio 35/55.

This predominance of sisters was seen even more clearly in the number being surrounded by sisters: 23, compared with only 8 being surrounded by boys.

In 111 fathers:

8 were only child, 33 were oldest, 27 youngest child.

The sib ratios showed a slight favouring of sisters: 28/42 and 35/41, thus clearly differing from alcoholic men's fathers.

The loss of parents ratio also displays a feminine preponderance being 5-1-12 and furthermore 23 were younger than their wives.

The number of investigated couples of

Maternal grandparents

is at present only 11. The maternal grandmothers had a majority of sisters.

It is worth mentioning that the case load of alcoholic men and their parents consists of three different groups:

- (1) 50 % from Danish upper and middle socio-economic groups, being private patients;
- (2) 25 % from Danish lowest socio-economic group, treated without any charge at out-patients clinics;
- (3) 25 % Non-Danish cases, these cases collected during visits to treatment centers in French Switzerland, Sweden, Norway, Iceland and California. The characteristic family pattern was found in all groups.

Further studies in the family background of the grandparents are proceeding.

Already, however, it may be claimed that family constellation analysis can to a large extent reveal those persons, who are most alcoholism-prone and those who almost certainly can never become alcoholics.

The applied standard analysis technique is described in *Martensen-Larsen. O.: Family constellation analysis and male alcoholism. Acta Psych. scand. suppl. 106, 241-247, 1956.*

Copenhagen, Denmark

THE FAMILY CONSTELLATION AND HOMOSEXUALISM

By O. MARTENSEN-LARSEN

Fathers to male alcoholics were found to be preceded or succeeded by brothers 1.5 times as often as by sisters. In alcoholic women we found that they themselves, their mothers and grandmothers were even more frequently surrounded by sisters, their sibships being rather unisexual. As these findings were particularly conspicuous in a few alcoholic women, who also had homosexual problems, we decided to analyse a group of well-defined homosexual people of both sexes. These were found in some social clubs for homosexuals in Copenhagen. The leaders as well as the members have been most friendly and cooperative.

In 63 homosexual men were 13 only child (more than twice the expected number). The oldest child/youngest child ratio was 6/26. Oldest brother/in-between brother/youngest brother ratio was 9-22-23. The distribution in upper/middle/lower thirds of the sibships was 9-9-32.

We feel inclined to say, that the homosexual men are preferably found in the rather dependant sib situations. An only child or a youngest child will never achieve much exercise in dominating other children.

The homosexual men had somewhat more frequently brothers than sisters, exactly as stated by *Theo Lang*. We, however, in 42 fathers and 21 Grandfathers found this tendency as well. Thus 11 fathers were surrounded by brothers, while only 3 by sisters.

In 45 mothers and 25 grandmothers the unisexual tendency in the sibships was even more pronounced. Thus 8 mothers were surrounded by sisters, while only one by brothers.

There is a slight tendency of the mothers being the younger sibs

(unlike the alcoholic men's mothers), while the grandmothers are very clearly recruited in the in-between sisters.

In 44 homosexual women, 39 mothers and 16 maternal grandmothers we find that their sibships present a clear unisexual tendency (preponderance of sisters) apparently most outspoken in the grandmothers.

The homosexual women tend to come from the upper or lower part of the sibship (as with alcoholic women). Their mothers most frequently are from the middle of the sibship, while the maternal grandmothers are found in the upper end of their sibship.

None of the 44 homosexual women had, before the age of 15, lost their real mother and kept their real father, while 9 had lost their real father and kept their real mother. This finding corresponds with the conditions in alcoholic women.

We believe the rather unisexual sibships surrounding the parents and grandparents of homosexuals further the development of abilities for making spiritual contacts between persons of the same sex. A homospirituality and homoaffinity is created but consequently also a reduced faculty of making contacts with the opposite sex. This state needs not at all to be linked up with any sensual, homosexual feelings.

If a child grows up, however, in a such homospiritual, non-heterosexual atmosphere its risk for developing the homosexual qualities seems very much increased.

The present study does not explain why unisexual sibships are found in some families. In a majority of cases we however believe that Homosexuality is a psychological result of children being brought up in an unhealthy unisexual atmosphere.

Discussion

E. Strömberg (Risskov, Denmark): The problems under discussion are no doubt interesting. The wealth of figures presented by Dr. *Martensen-Larsen* is not easy to evaluate, partly because a background consisting of the corresponding figures in the general population is not available. Such factors as age distribution of the populations considered must be accounted for, too. Problems concerning a propositus place in a sibship and concerning the sex-ratio in sibships are very intricate from a statistical point of view. *Theo Lang's* investigations, mentioned by Dr. *Martensen-Larsen*, are a good example of this. His theory of homosexuality was thought to imply the existence of an excess of males in the sibships of the homosexuals. Such excess was found, but later, it appeared that, if *Lang's* theory were correct, no excess should have been found.

Donauwörth, Deutschland

ERBBIOLOGISCHE PROBLEME BEI DER JUGENDKRIMINALITÄT. KRIMINOLOGISCHE UNTERSUCHUNGEN AN 500 JUGENDLICHEN KRIMINELLEN

Von J. DEUSSEN

So wahr es ist, daß der Mensch nicht nur einen Körper besitzt, sondern auch eine Seele, so wenig – scheint es – hat man von seiten der Erbbiologie der Besonderheit dieses Tatbestandes bisher Rechnung getragen oder tragen wollen. Es erhebt sich die Frage, ob man bei der Erbbiologie der psychischen Eigenschaften und Erscheinungen, d. h. also bei der *Erbpsychologie* dem Materialismus zwar abgeschworen, ihn aber noch nicht überwunden hat. Sollte man noch heute die Seele im Grunde als ein «Sekret des Gehirns» ansehen oder ansehen wollen? Auf ein solches Ziel könnte die Hoffnung hinweisen, z. B. bei Intelligenzprüfungen eine *Methode* der Forschung anzuwenden, die «den Grad der Erblichkeit komplexer Eigenschaften wie Eiproduktion bei Geflügel oder Milchleistung bei Kühen zu bestimmen» gestattet [1]. Auch wird hinsichtlich des *Materials* der erbbiologischen Forschung nicht mit genügender Schärfe ein prinzipieller Unterschied zwischen körperlichen und seelischen Phänomenen beachtet. Dies läuft dann darauf hinaus, daß es «die Aufgabe der Erbpsychologie bleibt, die leibliche ‚Unterlage‘ für die von ihr beobachteten seelischen Erscheinungen aufzuspüren und in ihrem Erbgang zu erforschen», wie ich dies selbst früher als Nahziel angenommen habe [2]. Der hiermit eingeschlagene Weg erwies sich jedoch inzwischen als nutzlos, wenn wir wirklich Erbpsychologie treiben, d. h. eine eigenständige Forschung auf diesem Gebiet aufbauen wollen.

Wir müssen mehr, als es bisher geschah, den Tatsachen Rechnung tragen und *Leib* und *Seele* als zwei wohlunterscheidbare Seiten am Sach-

verhalt der organismischen Natur, d. h. an jedem Individuum betrachten. Allerdings sind Leib und Seele auch wieder untrennbar miteinander verbunden, und zwar im Sinne einer Polarität. Hierunter verstehen wir eine Wechselbeziehung, bei der einmal mehr der eine, das andere Mal mehr der andere Pol dominiert; andere Definitionen des Leib-Seele-Verhältnisses führen zu Widersprüchen.

Für die Vererbung leiblicher Merkmale und Vorgänge gibt der Begriff des Gens die Grundlage ab. Der Versuch, in Korrespondenz hierzu, den Begriff des Erbradikals aufzustellen, mißlang vermutlich deshalb, weil er inadäquaten, materialistischen Vorstellungen entsprach. Bereits die leibliche Vorgänge betreffende, quantifizierende und messende Genetik war nicht imstande, die sog. Maschinentheorie des Lebens zu verifizieren. Sie griff gern zu Ausdrücken, wie «Abbild» und «Reproduktion» (*Stern* [3]), Prägung und Lenkung u. ä., um die Wirkungsweise der Gene letzten Endes verständlich zu machen, wenn sie nicht mit dem Hinweis auf noch unbekannte chemische oder hormonale Steuerung Scheinlösungen anbot oder sich gegenwärtig fast darin überbietet, mit Hilfe der Mathematisierung den gefährlichen Entsinnlichungsprozeß der Naturwissenschaften zu fördern. Andererseits wußte die Erbpsychologie nicht – soweit sie überhaupt selbständig in Erscheinung trat –, wie sie mit der Analyse des «Erbgedächtnisses» (*Jordan*) vorankommen sollte. Weder Stammbaum- noch EZ-Untersuchungen förderten im wesentlichen eindrucksvollere Tatsachen ans Licht, als etwa das bereits bekannte Phänomen, daß eben auch psychische Vererbung angenommen werden muß. Dabei läge es gerade im Vermögen der Erbpsychologie, den bisher von der Naturwissenschaft, insbesondere der Atomphysik, fast bis zum Exzeß des Selbstmordes beschrittenen Weg der Naturbeherrschung zu verlassen und sich dem uns viel notwendigeren Naturverständnis zuzuwenden. Dies Versagen der gesamten Psychologie, die Naturvorgänge in erster Linie verständlich zu machen und sie nicht mit der mehr-weniger bewußten Absicht zu betrachten, sie dem menschlichen Machttrieb zu unterwerfen und sie auszunützen, liegt nicht – wie man zunächst meinen möchte – daran, daß es sich bei seelischen Phänomenen lediglich um kompliziertere Sachverhalte handelt, die etwa als «quantitativ abgestufte Eigenschaften» zu ihrer Interpretation eines polyfaktoriellen Erbganges bedürften [4], sondern daran, daß hier *Qualitätsunterschiede* innerhalb einer Ganzheit vorliegen, die sich allein durch Evidenzurteile erfassen und deuten lassen.

Die Schwierigkeiten vermehren sich für den Erbpsychologen noch dadurch beträchtlich, daß er es beim Menschen außerdem mit *geistig* bestimmten Sachverhalten zu tun hat. Er befindet sich also nicht in der glücklichen

Lage, wie etwa die Tierpsychologie, die gegenwärtig erfolgversprechende Untersuchungen über die Psychomotorik betreiben kann (*Lorenz*) und dabei unmittelbar vom Verhalten auf seelische Inhalte schließt.

Seit Beginn der erbpsychologischen Forschungen spielt die *Kriminalbiologie* eine besondere Rolle, da man annahm, in einer spezifischen kriminogenen Anlage wenn nicht auf eine «Krankheit» – welche These bald fallen gelassen wurde –, so doch möglicherweise auf ein wohlcharakterisiertes «Erbradikal» zu stoßen. Man glaubte vielleicht, daß uns dies Erbteil aus der Zeit der vorgeschichtlichen Menschheit bis in die Gegenwart begleitet habe, – als ob es in einer wohlgesitteten Gesellschaft nur noch gleichsam als *Relikte* Verbrecher gäbe, die so handelten, wie es bis jetzt bloß mehr den Staaten untereinander erlaubt zu sein scheint.

Für eine solche Auffassung des Verbrechens und der Verbrecherpersönlichkeit fand ich keine Bestätigung. Im vorliegenden handelt es sich um eine 1955/56 durchgeführte kriminologische *Untersuchung* an etwa 500 schwerstkriminellen Jugendlichen männlichen Geschlechts im Alter von 14 bis etwa 21 Jahren, die sich in der Jugendstrafanstalt Bayerns – einem Land mit etwa 9 000 000 E. – befanden. Ein Jahresquerschnitt wurde dadurch gewonnen, daß die Zahl der Zugänge und der Abgänge etwa die Hälfte der untersuchten Verbrecher beträgt. Während bei der Untersuchung der Kriminellen keine Auslese getroffen wurde, stellen diese selbst eine Auslese von etwa 0,5 % der insgesamt in einem Jahre wegen Verbrechen und Vergehen gegen deutsche Strafgesetze belangten Jugendlichen gleichen Alters und Geschlechts (1955: 48 102) dar. Erst wenn alle anderen Besserungsmittel im Sinne des heute im Bundesgebiet herrschenden Erziehungsstrafvollzuges versagten, kamen die untersuchten Jugendlichen ins Gefängnis. Sie waren bei einer nur etwa 5 J. umfassenden Beobachtungszeit in etwa 75 % rückfällig oder wurden rückfällig, wobei die tatsächliche Prozentzahl, abgesehen von der «Dunkelziffer», wesentlich höher liegen dürfte. Wir haben bei unserem Material also sog. Hangverbrecher vor uns, die nach einer häufig im Urteilsspruch anzutreffenden Formulierung aus «unwiderstehlicher, schädlicher Neigung», d. h. also mehr aus Anlage als aus Umwelt-bedingten Gründen verbrecherisch handelten; gewiß eine seltene und auch nicht leicht zugängliche Auslese für den Kriminalbiologen.

Nach der für unsere Zwecke allein brauchbaren polizeilichen *Kriminalstatistik* [5] wurden 1955 in Bayern absolut 339 781 Straftaten gezählt, was einer Kriminalitätsbelastungsziffer von 3,8 % entspricht. Insgesamt wurden 3,13 % der Bevölkerung straffällig. Das polizeiliche Aufklärungsergebnis wird mit 83,7 % angegeben. In zunehmendem Maße interessiert die Verbrechensintensität der Jugendlichen bzw. der sog. «Halbstarken» die

westliche Welt. Die damit zusammenhängenden Sorgen erscheinen auf Grund meiner Untersuchung und der Statistik berechtigt, insbesondere dann, wenn man die nach dem neuen JGG. sog. «Heranwachsenden» (Hw.) im Alter von 18–21 J. berücksichtigt. Während 1955 der Bevölkerungsanteil der Kinder in Bayern beiderlei Geschlechts 20,6%, der Jugendlichen (14 bis 18 J.) 7,6%, der Hw. nur 4,9% und der Erwachsenen 66,9% betrug, war der Anteil dieser Gruppen an den polizeilich bearbeiteten Verbrechen und Vergehen 1,7, 7,1, 7,9 und 83,3%. Damit übertreffen die Jugendlichen im Alter von 14–21 J. die für ihre gute Erziehung verantwortlichen Erwachsenen erheblich an Kriminalität, wobei das Verhältnis von männlichen und weiblichen Tätern (86%:14% bei einem Bevölkerungsanteil von 46,4%:53,6% i. J. 1955) relativ konstant bleibt und eine geringe Korrektur durch reisende Täter (4,9%) und Ausländer (2,9% bei einem Bevölkerungsanteil von nur 1,3%) erfolgt. Jeder 6. Verbrecher ist also ein Jugendlicher! Würden die Erwachsenen im gleichen Umfang wie die Hw. straffällig, würde es in Bayern etwa 100 000 Kriminelle im Jahre mehr geben! Soweit man vom Delikt auf den Täter schließen kann, bessert sich das Bild nur scheinbar, denn immerhin finden sich unter der Rubrik «Mord und Totschlag» schon 1% Kinder und 4,1% Hw., unter «vers. Mord. und Totschlag» 5,2% Hw., unter «Kindstötung» 22,2% Hw. (nur w. mit einer Zunahme gegenüber 1954 von 26,7%), unter «fahrl. Tötung» 7,9% Hw., unter «Körperverl. m. tödl. Ausgang» 8,5% und unter «gef. u. schw. Körperverl.» sogar 12,7% Hw. Wegen der Höhe der damit verbundenen Strafe – immerhin beträgt die Höchststrafe bei Mord nach dem JGG. nicht mehr als 10 J. Gfgs., wovon durchschnittlich etwa die halbe Strafzeit auf Bewährung erlassen wird – befinden sich die genannten Schwerkriminellen sämtlich unter dem vorliegenden Material. Allerdings liegt die Domäne des jugendlichen Verbrechers beim Diebstahl (Zunahme gegenüber 1954 6,6%), bei welchem Delikt alle Jugendlichen (inkl. Kinder) mit 40,8% und bei der vors. Brandstiftung, wo diese sogar mit 48,2% beteiligt waren. Erwähnt mag noch werden, daß auch die Selbstmordziffer, die gegenwärtig im Bundesgebiet mit etwa 12 000 Fällen den Stand der Tbc-Mortalität erreicht hat, bedenklich erscheint, zumal sich unter den Selbstmördern eine Anzahl von Fällen befinden dürfte, bei denen sich die Aggression statt gegen die soziale Umwelt gegen den Täter selbst richtete: in Bayern verübten 1955 3 Kinder und 47 Jugendliche im Alter von 14–18 J. Selbstmord.

Bekanntlich spielt die *Methodik*, mit der erbpsychologische Untersuchungen durchgeführt werden, eine bedeutsame Rolle. Gerade auf einem Gebiet, auf dem zur Feststellung qualitativer Unterschiede Evidenzurteile ausschlaggebend sind, kommt alles darauf an, daß die Methodik logik-

wissenschaftlichen Ansprüchen genügt und – von verschiedenen Untersuchern angewandt – zu gleichen Resultaten führt. Ich habe bei der Untersuchung nichtseßhafter Asozialer [6] eine solche Methode entwickelt und muß darauf verweisen [2]. Im vorliegenden Fall wurde eine ausführliche und mit der Exploration verbundene subjektive Anamnese und auf Grund der Jugendamts- und Gerichtsakten die objektive Vorgeschichte erhoben. Der körperliche Befund umfaßte die anthropologischen, internen und nervenärztlichen Daten, beim psychischen Befund fanden die bekannten psychologischen und psychiatrischen Methoden Verwendung, wobei zur Objektivierung die Beurteilung durch eine Graphologin und durch geübte Strafvollzugsbeamte (Kriminalpsychologen und -Pädagogen, Geistliche und Aufsichtsbeamte) beigezogen wurde. Die erbbiologischen Verhältnisse ließen sich – da hierfür leider nur beschränkte Mittel zur Verfügung standen – bloß bestmöglich mit Hilfe der Befragung und Exploration von Verwandten und Beziehung entsprechender Akten klären. Sämtliche Kriminelle konnte ich längere Zeit während ihres Strafvollzugs beobachten.

Als *Resultat* der Untersuchung ergab sich unter Berücksichtigung der Durchschnittsuntersuchungen von *Thomae* u. a. ein sog. Punktesystem, nach dem sich die Gefahr eines baldigen kriminellen Rückfalls abschätzen ließ. Hierbei blieb der ebenfalls wirksame Umweltfaktor (Strafbestimmungen, Polizeiverfolgung) als kriminalbiologisch nicht erfaßbar außer Ansatz. Offenbar wird aber durch das Strafgesetz nur der in jeder Beziehung unbegabteste und disharmonisch strukturierte Teil der Bevölkerung in erster Linie betroffen, was besonders deutlich bei der Jugendkriminalität erkennbar erscheint. Jedenfalls dürfte ein «Punktesystem» die bisher einzige Möglichkeit darstellen, die Schwere eines Falles hinsichtlich seiner «kriminellen Neigung», d. h. also nach seiner vermuteten kriminellen Anlage unter Verzicht auf vereinseitigende Typologien sichtbar zu machen. Nach wie vor gilt ja der Satz des verdienstvollen Begründers der Kriminalbiologie *A. Lenz*, wonach diese «die Ermittlung des Zusammenhanges zwischen Persönlichkeit und krimineller Tat» zum Ziel hat [7]. Nicht adäquat der jeweiligen Persönlichkeitsstruktur ist die in früheren Arbeiten immer wieder versuchte Einteilung nach den Deliktarten. Dieses Ergebnis war aber zu erwarten, da bei dem zur Verurteilung benützten Maßstab des Juristen, der in erster Linie ja die *Tat* wertet, durchaus formale Gesichtspunkte bzw. soziale Umweltfaktoren ausschlaggebend sind. So vermag also in kriminalbiologischer Hinsicht die *Person* eines Mörders durchaus eine bessere Prognose zu haben als die eines kleinen Rückfalldiebes. Im einzelnen können die prognostischen Kriterien hier nicht aufgeführt werden. Nicht ohne weiteres den bisher bekanntgewordenen kriminologischen Erfahrungen

entsprachen Ergebnisse, die aus der Auslese des Materials verständlich werden. Während der körperliche Gesundheitszustand, Geschlechtstrieb bzw. Fertilität und die körperliche Leistungsfähigkeit der untersuchten Kriminellen über dem Durchschnitt gleichaltriger Nichtkrimineller lag (!), fand sich bei 72 % eine Schwäche der sog. höheren Intelligenz (die von der sog. praktischen Intelligenz mehr, als es bisher geschieht, unterschieden werden sollte und hier zwischen sog. physiologischer Dummheit und mittelschwerer Debilität lag) und nach vorsichtiger Schätzung bei etwa 50 % schwere Psychopathie. Geisteskrankheit bzw. Verdacht auf Geisteskrankheit spielte keine Rolle (3 Fälle). Das Vorliegen von Psychopathie ließ sich deshalb schwer bestimmen, weil wir gewohnt sind, diese an einem deutlich erkennbaren Übermaß oder Fehlen bestimmter Charakteranlagen zu diagnostizieren. Fast 90 % der Kriminellen besaßen jedoch eine derart undifferenzierte («primitive») Charakterstruktur von so geringem Formniveau (*Klages*), daß selbst Psychopathien bei ihnen – da von einer «Diminutivperson» ausgehend – oft innerhalb der sonst zu beobachtenden Schwankungsbreite von Charakteranlagen fielen. Auf Grund des neuen JGG. sind ggf. sog. Reifeentscheidungen dahingehend zu fällen, daß ein Hw. im Alter von 18–21 J. trotz körperlich entsprechender oder accelerierter Entwicklung noch psychisch einem Jugendlichen zwischen 14 und 18 J. gleichgestellt wird. Meistens lag in dem untersuchten Material jedoch eine seelische Undifferenziertheit konstitutionell im Sinne einer allgemeinen Charakteranlagenschwäche vor, so daß bei diesen Kriminellen eine psychophysisch gleichlaufende Entwicklung oder auch Acceleration bestand und man auf das «Ausreifen» der seelisch-geistigen Funktionen vergeblich warten mußte. In einer geringeren Anzahl von Fällen fand sich eine Parallele zwischen infantiler Körperbildung und undifferenziertem («infantilem») Wesen. Einen gewissen «Idealtyp» des jugendlichen Schwerstkriminellen stellten die Landfahrer (*Jenische*) dar. Weiterhin fielen charakterlich und auch erbbiologisch zwei «Typen», und zwar im Verhältnis von 58 %:42 % mit nur 10–15 % Streubreite auf: Die Aggressiven mit gewisser Brutalität und Störrischkeit einerseits und die Mitläufer aus Faulheit, Beeinflußbarkeit und Phantasterei andererseits. Familiär besteht in den in Frage kommenden Generationen gegenwärtig eine erhebliche Zerrüttung, die aber im Sinne der Kriegsfolgen weitgehend exogen bedingt sein kann. Doch ist seit 1954 eine gewisse Konsolidierung eingetreten, so daß bei den 1955/56 untersuchten Kriminellen im Unterschied zur Zeit unmittelbar nach 1945 auch erbbiologisch das Hangverbrechertum mit entsprechender Belastung in den Sippen so weitgehend vorherrscht, wie es wohl an keiner anderen Stelle der Fall ist. Nicht unerwähnt soll zum Schluß bleiben, daß

ich hinsichtlich des Leib-Seele-Zusammenhanges trotz dieses einzigartigen Materials vor demselben Problem stand wie in der Sexualpathologie [8]: Eine genügend evidente Konkordanz zwischen dem anthropologisch erfaßbaren Erscheinungsbild des Hangverbrechers und der Intensität seiner «kriminogenen Anlage» bestand nicht. Allerdings überwogen körperlich etwas die sog. Primitivmerkmale, und die Prognose verschlechterte sich bei Dysplasien und aggressiv oder infantil wirkenden physiognomischen Merkmalen.

Folgende Thesen ergaben sich aus der vorliegenden Untersuchung:

1. Wir unterscheiden beim Menschen vererbare leibseelische und seelisch-geistige Anlagen; jene lassen mendelistische Erbgesetze erkennen, diese erlauben nur eine statistische Behandlung im Sinne der *empirischen Erbprognose* (Rüdin). Die Postulierung psychischer Erbradikale in Analogie zur körperlichen Mechanik ist rein spekulativ.

2. Voraussetzung erbpsychologischer Forschung bildet eine bei allen Untersuchern übereinstimmende, bei Nachkontrollen durch andere Untersucher dieselben Resultate ergebende *Methodik* und eine gleichmäßig von allen Untersuchern angewandte, auf übereinstimmenden Definitionen beruhende *Systematik* hinsichtlich der menschlichen Persönlichkeitsstruktur. Diese Voraussetzungen sind gegenwärtig noch nicht vorhanden.

3. Aus verschiedenen Gründen wurde zwar seit langem eine «kriminogene Anlage» vermutet, doch konnte diese erbbiologisch bisher weder isoliert werden, noch erscheint sie – zumindest beim Stande der gegenwärtigen Forschung – allein schon wegen ihrer *Ubiquität* und *Komplexität* isolierbar.

4. Zur genaueren Bestimmung der kriminellen Prognose im Sinne von A. Lenz läßt sich mit Vorteil ein «*Punktesystem*» anwenden, das geeignet ist, den Begriff des Kriminellen genauer zu bestimmen und als Beobachtungskriterium zu dienen. Hierbei kann die erbbiologische Diagnose zur Herausarbeitung der psychologischen Struktur nicht entbehrt werden, dagegen erscheinen formaljuristische Unterscheidungen wenig brauchbar.

5. Was wir unter dem Typus des Hang-, Gewohnheits- oder *Anlageverbrechers* verstehen, ist eine Kombination von Charakterabartigkeit (Psychopathie und Schwachsinn), Undifferenziertheit («Primitivität») und kriminogenem Anlagekomplex, bei dem negativ gerichtete, allgemeine Wertgefühle (negativ gerichtetes Ethos), Gemütsarmut bis zur Bindungslosigkeit und Antriebsschwäche bzw. -Disharmonie in Form einer mehr antisozialen (aggressiven) oder mehr asozialen (passiv-labilen) Störung der Ich-Umwelt-Beziehung eine Rolle spielen, jedoch Umweltfaktoren in oft erheblichem Ausmaß beteiligt sind.

6. Insgesamt dürften *kriminalbiologische Untersuchungen* einen z. Z. geringen Wert für diejenige erbpsychologische Forschung besitzen, die auf die Herausarbeitung rein psychischer Vererbungsgesetze ausgeht. Um so größeren Wert kommen ihnen für demographische und bevölkerungspolitische Erkenntnisse zu, da das Gewohnheitsverbrechertum wohl die geringwertigste, gleichzeitig aber auch gefährlichste Menschengruppe mit relativ hoher Fortpflanzungsrate innerhalb eines Volkes darstellt und mit seinen dem Strafgesetz nicht mehr erreichbaren, höherdifferenzierten und begabteren Vertretern imstande sein dürfte, die gesamte staatliche und soziale Ordnung zu zersetzen.

7. Die *Jugendkriminalität*, von deren schwerster Form wir bei unserer Untersuchung ausgingen, stellt nicht nur gleichsam den «Kern» des Hangverbrechertums dar, sondern läßt sich auch als Index für die gesamte Kriminalität einer Bevölkerung in einem gewissen Zeitpunkt verwenden. Ihre gegenwärtige quantitative und qualitative Zunahme erweckt begründete Sorgen und erfordert praktische Konsequenzen, wie es überhaupt an der Zeit sein dürfte, daß das «Material» Mensch eine pfleglichere Behandlung erfährt, als ihm bisher von Staats wegen geschenkt wurde.

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EPIDEMIOLOGICAL CONTROL OF HEREDITARY DISEASES

Genetic-Hygienic Registration Medico-Genetic Ascertainment

Panel Discussion

August 6, 1956

Tage Kemp (Copenhagen): Many attempts by various methods have been made to estimate the incidence of hereditary defects and diseases in various countries or groups within populations. Some information concerning the incidence of hereditary diseases was obtained centuries ago through vital and medical statistics, yet health services are still collecting material elucidating this question.

Direct investigations concerning the problem have been carried out for the most part during the last fifty years, originally on mental defects and diseases, but later within the whole field of medicine.

Several types of methods have been used to investigate the morbidity in the average population and to ascertain the amount of hereditary tainting, as, for instance, census investigations, sampling methods, and morbidity, mortality and hospitalization statistics. These methods may be used in various ways:

Sampling methods are often applied combined with proband materials or propositi investigations; and it must be considered whether the sample is representative of the average population and fulfils certain assumptions with regard to selection and composition.

Census investigations may include greater or smaller geographical units, states, counties, municipalities, communities, islands, valleys and so on, or population-groups delimited according to sex, profession, social class, race, nationality, etc.

Various age groups may be examined, for instance, new-born, school-children, military conscripts or certain age classes; or mortality statistics may be used.

By determining the number of individuals within a group presenting a hereditary disease with a limited period of manifestation, we get information on the prevalence of the disease in the population. As a rule it

is, however, a matter of greater interest to find the probability of each individual getting the disease if he lives through the whole risk zone, i.e., to find the morbid risk (or the morbidity risk or the expectancy [Krankheitserwartung]) for the disease concerned in the population. But in calculating the morbid risk, consideration must be taken both of the age at onset of the disease and the age distribution in the group examined. In the individuals who have not yet reached the risk zone, all have a full chance of getting the disease later in life. Those who are in the midst of the manifestation period have a certain, though smaller, chance of getting the disease, decreasing with increasing age; and only for those who are old enough to have passed the entire risk zone is the morbid risk nil. The morbid risk may be calculated as the cumulative incidence of the disease for all age groups until the end of the period of manifestation.

During recent years new possibilities have been created for investigations on the frequency of hereditary diseases in the population in countries or regions where a medico-genetic or genetic-hygienic registration has been established. A medico-genetic registry includes a systematic registration or card-index covering all the patients in the region or country concerned who are afflicted with a serious hereditary affection, and also their families.

In the medico-genetic registry we have the starting point for more thorough studies into particular fields, in many instances of the inheritance of a special lesion or disease. The procedure then is as follows: A physician, who is trained as a specialist in the field concerned, makes a thorough investigation of the individuals with the disease or lesion in question and of their families, partly on the basis of hospital records, other documentary material and genealogical investigations, partly by travelling about, visiting and examining the individual patients in their homes or by calling the patients to an institution or to some hospitals for observation and more thorough investigation.

Through the studies of the various diseases and lesions their mode of inheritance, their etiology and pathogenesis, their clinical picture, their frequency and geographical or social distribution in the population, the possibilities of their treatment and prevention, and the effective fertility of the affected can be investigated.

On the basis of the registration it will be possible to investigate whether the hereditary diseases often arise through mutation. The mutation rate can be calculated, and the causes of mutation can be considered. The manifestation penetrance and expressivity of the pathological dominant or recessive genes can be estimated. Conditioned dominance and polymerism in morbid inheritance can be studied and the effects of selection, mutation,

intermarriage, isolates, assortative mating, genetic drift and lethal genes in the population can be investigated.

Using the experiences gained in the medico-genetic registry it will be possible to exercise a genetic-hygienic or eugenic activity as adviser on questions of sterilization, induced abortion, marriage, adoption and special relief.

The only way to follow and control and study the whole body of hereditary lesions in a population is through a permanent systematic and thorough medico-genetic or eugenic registration comprising all important hereditary affections in the populations. If in a given case the question of genetic-hygienic measures is raised the registration may furnish information about the person or persons in question and their families. It will thereby in many cases be much easier to give an advice.

For the problems of radiation genetics the epidemiological control of hereditary diseases is of fundamental importance. In the future it will be necessary from the point of view of preventive medicine to follow and control the serious hereditary diseases in the population, and for that purpose a medico-genetic epidemiological control by means of a genetic hygienic registration will be an indispensable remedy.

Ø. Ødegård (Oslo): The use of the term "epidemiology" in connection with non-infectious diseases needs an apology. The original meaning of epi-demic, however, is merely "something which is inflicted on the people", and that is true of schizophrenia and hemofilia as well as of yellow fever.

For the study of the distribution of diseases in various parts of the population epidemiology makes use of *demographic* methods, and so it might be regarded as a special field within the wider one of demography ("pathological demography"). Epidemiology is also related to *ecology* in that it studies the relations of human beings to their environment, but in ecology this is done by a wider range of methods.

In human genetics epidemiological methods have to be introduced as soon as one proceeds beyond the study of individual pedigrees. Weinbergs method of counting the relatives of probands is a classical example. It is based upon the epidemiological fact that the incidence of psychoses varies

with age. Weinbergs method was rather primitive, because it did not utilize all the known facts about the age distribution of psychoses, and Strømgrens modification is (at least in psychiatric genetics) the first example of the use of adequate epidemiological methods in human genetics.

Now age is not the only variable which is of importance in this connection. Differential *mortality* was recognized rather early. Somewhat later came *marital condition*: The incidence of schizophrenia is four times as high in the single as in the married, and consequently married groups (such as parents) are not directly comparable with mixed groups such as siblings without due correction. *Migration* is important, because it leads to differentials in consanguinity, in morbidity, etc. *Geographical distribution* has a similar influence, *occupational* differentials are coming into the picture, and many others.

Epidemiology is a science in its own rights, with special application to the nature-nurture problems. But one of its functions is to furnish human genetics with the statistical foundation which it needs in order to avoid serious errors. Incidentally epidemiological registration can help genetics in the collection of cases, but this is in my opinion far less important.

In epidemiological research one faces the dilemma that one needs a material which is very large, but at the same time very carefully examined. My own recent studies of the incidence of psychoses in different occupations showed for instance that for this purpose at least 25,000 patients were needed. The obvious solution is to use extensive as well as intensive methods. Intensive studies of the entire population of a restricted area (*Bremer, Essen-Møller, Sjøgren* et al.) have the advantage of complete registration of even minor pathological conditions. On the other hand the relatively small number of cases is a drawback, and the findings in one special area may not be typical of the population as a whole.

Registration on a national basis is, therefore, a necessary supplement. No such registration can be complete in the absolute sense of the word, but within the limits of certain given definitions it can be sufficiently complete to avoid bias due to selection. While one can never register all cases of schizophrenia, one can easily get all schizophrenics who are admitted to certain hospitals. A large-scale registration can hardly be carried out on an altogether voluntary basis, but has to be enforced by some central authority. This does not exclude friendly co-operation, but makes it essential that the epidemiologist show a certain tactical discretion. One should for instance not ask for too many details, as this might lead to irritation, and to incomplete data. In Norway central registration of all admissions to mental hospitals has been going on for twenty years without any serious

conflicts with the hospitals and without a single complaint from patients or relatives.

A national registration of diseases should be based upon *first admissions* (to hospitals or to other types of medical care). *Prevalence data* are useful only when the group is so small that the cases can be followed individually, for instance by morbidity tables. Even admission statistics are frequently misleading, however, particularly in regions where medical care is underdeveloped or of relatively recent origin. A nation-wide registration will not give reliable incidence data until a fairly stable equilibrium has been maintained for some time. Under favourable circumstances admission statistics and census investigations of small areas lead to surprisingly similar results, but both methods have special advantages.

The combination of intensive and extensive methods is frequently advantageous. In Norway we found an excessive mental morbidity in seamen. So a sample of the total material was selected for closer scrutiny of the case histories—for instance with regard to possible errors in the statistical registration, etc. Much additional information was obtained, and the statistical findings were largely confirmed.

Diagnosis is a problem in registration work, particularly in psychiatry. By a systematic follow-up of the first-admissions through all successive discharges and re-admissions many initial mistakes are corrected. But the main thing is to reach an international agreement. The adoption of a universal nomenclature (like that of the W.H.O.) is merely the first step. The terms have to *be used in a uniform way* by the hospitals and the doctors concerned. At least in psychiatry this is not the case, and a certain amount of resignation from the part of particularly individualistic colleagues or schools of thought is to be wished for. After all diagnosis is merely a means of communication, and does not preclude personal conviction about the nature of the diseases.

J. Mohr (Oslo): I shall try to describe in a few words our work at the Human Genetics Laboratory of the Oslo University to establish a continuous registration of various diseases that may be hereditary, in the Norwegian population. The registration is carried out in co-operation with the Public Health Services and the Central Bureau of Statistics. Financially, it is supported by the Rockefeller Foundation and the Norwegian Research

Council. The work got really under way only about a year ago, when we obtained the necessary financial support, so our experience is still limited.

The general plans have been rather similar to those of the Danish register at the University Institute of Human Genetics here in Copenhagen. This register has to a large extent served as a model. We have until now taken steps to register mainly the following general groups: blindness, deafness, mental defect and external malformations. Outside these groups we have mainly received reports on various conditions due to single genes, for instance albinism, hemofilia and hemolytic jaundice.

In the case of blindness, deafness and mental defect a reporting system has now been established although of course a number of improvements and developments remain to be carried through. In the case of external malformations we expect reporting to start January 1, 1957, at which date new birth certificates are supposed to be introduced.

Further, we are establishing at the Institute a register of all twin births in Norway (or rather plural births) and finally, in co-operation with the office for Psychological Testing of Military Personnel, a registration of cousin marriages among parents of persons who are being examined prior to military service.

In general we have not aimed at an immediate registration of all cases in the population, as this would have given more reports than we could possibly handle. We have rather aimed at a registration of newly diagnosed cases.

Sources of information. Concerning the sources of information, regular reporting of various kinds has so far been established from the following 7 institutions or persons:

(1) *The Central Office for Special Schools.* This office sorts under the Ministry of Education and has to do with special education of individuals who are unable to profit by the teaching in the regular schools.

According to Norwegian act of 23rd November 1951, all such children have to be reported to the Central School Authorities, who convey reports to the Central Office for Special Schools. Most of these children are either blind, deaf or mentally defective. Most of the latter are feeble-minded, with I. Q.'s in the range 50-70.

When a child is referred to a certain school, the Central Office sends a notice to the local school authorities. The Human Genetics Laboratory receives a copy of each such notice, which means that the heredity register is kept informed about every child reported to the Central Office for Special Schools.

This arrangement was put into effect a little less than a year ago, namely on September 1, 1955. Up to July 20th this year we have received information from this source on 394 children with mental defect, 23 with blindness, 25 with deafness and on 126 with language difficulties (namely difficulties of reading, writing or speech), reports on 468 children in all.

It may perhaps be of interest to bring these numbers into relation with the number of Norwegian children who reach school age every year, which is about 60,000. The reported children with mental defect (as stated chiefly feeble-minded) constitute 0.66 per cent of this number, the blind 0.38 per thousand, the deaf 0.42 per thousand and those with language difficulties 0.21 per cent.

(2) *The Special Schools.* From the Central Office for Special Schools we get little more information than name, date and place of birth, and a very short diagnosis of each reported child. Further information is given by the Special Schools, where examinations or tests are carried out before teaching is started. Copies of these test—or examination reports are sent to the heredity register.

The Special Schools also possess some information on the families of the reported children. We expect to obtain reliable information concerning the parents and sibs with respect to such data as name, date and place of birth, and residence. We also eventually hope to obtain the name and birth dates of the grand-parents of the mother and father, in order to get reliable information concerning cousin marriages (a simple question as to whether the parents are related or not will scarcely give reliable answers).

(3) *The Central Register for Low Grade Mental Defect.* A third important source of information is the Central Register for Low Grade Mental Defect, at Emma Hjorths Hjem, Sandvika, near Oslo. This institution receives applications for admittance to the institutions for low grade cases of mental defect, that is idiots and imbeciles.

While the Special Schools for the feeble-minded sort under the Ministry of Education, the institutions for the low grade cases are in the care of the Public Health Authorities, that is to say the Ministry of Social Affairs. There is thus a sharp administrative division, and a corresponding division of information on cases of mental defect.

An arrangement has been made with the Central Register for Low Grade Mental Defect, under which information is regularly conveyed to the heredity register. This is done simply by making carbon copies of cards written out at the Register for Low Grade Defect.

(4) *The District Medical Officers.* A fourth source of information has been the District Medical Officers, who have given reports on various monomeric conditions, and on some cases of blindness and deafness.

While the sources for information mentioned previously will report all the cases they handle, only a small fraction of the cases handled by the district physicians will of course be reported. This presents a difficult practical problem. The effectiveness of this kind of reporting, where the physicians have to select the cases to be reported out of a large number of irrelevant cases, may easily be very low.

(5) *Hospital Departments.* The same problem arises as regards reports from Hospital Departments. Some special departments, such as those of neurology, dermatology and ophthalmology, handle a large number of cases which ought to be included in a heredity register. But in practice it would be difficult to get efficient reporting by asking only for these relevant cases. At present we get regular reports from only one hospital department, the Neurological Department of the State Hospital in Oslo. The reporting is done simply by making an extra carbon copy of every epierisis written out for patients of the department. The selection of relevant cases is made at the Heredity Register.

(6) *The Central Bureau of Statistics.* From the Central Bureau of Statistics we obtain information on twins. For its own purpose the Bureau of Statistics has every year since 1946 for each pair of twins (or rather for each plural birth) filled up a special form which happens to contain the information we need. We convey this information to the heredity register simply by borrowing the filled-up forms for the year, and transferring the data to index cards. Two sets are made, one for alphabetical arrangement and one for arrangement according to date of birth.

(7) *The Office for Psychological Testing of Military Personnel* gives information on cousin marriages. During the psychological testing to which all males are subjected before entering military service, a form has to be filled up by the testee, and into this form the psychologists have been kind enough to insert a question as to whether the parents of the testee are first cousins. The psychologists feel the procedure of filling up the forms is such that the answers to this question will probably be quite reliable. But it will of course be necessary to make special studies of the accuracy of the answers.

Uses of the heredity register. The possible applications of the register can of course only be described in rather general terms, in somewhat the same manner as a description of the uses of an institute of human genetics.

For purposes of research the register can be of assistance in various ways: As a starting point for studies of the familial distribution of various diseases and defects, and of their population genetics—selection, assortative mating, isolation, consanguinity. The registration of cousin marriages will provide a chart of the frequencies of such marriages in the various parts of the country and show changes of these frequencies as time passes. Besides being of interest in itself, this chart will be valuable as a standard of comparison in studies where the frequencies of cousin marriages among the parents of affected individuals are considered.

The registered cousin marriages may also be of interest as a starting point for studies of defects of various kinds among the offspring from such marriages. This may give information on the frequencies of deleterious recessives in the population, which is of particular interest in the atomic age, since it concerns the genetic sensitivity of the population to ionizing radiation.

In the case of single gene conditions, the register may be of aid in studies of genetic linkage and of frequencies of spontaneous mutation. Such a continuous registration would be the most direct way to detect possible increases in the frequencies of spontaneous mutations, such as might be expected if the irradiation of the population should increase substantially.

The register may also help to obtain unbiased series of twin pairs, for evaluations of the relative importance of heredity and environment to the development of the conditions concerned. Since we have a continuous register of twins, it is possible easily to check all the registered patients as to whether they are twins or not. Twins of the pathological category under consideration may then be examined in co-operation with the appropriate medical institution. This institution may take care of the clinical examination, while the human genetics laboratory examines the pair with respect to zygosity.

The register will also help to give more accurate knowledge of the distribution of various conditions in the population. From a practical point of view, the register will be of value as a source of information in genetic counseling. Information on relatives given for instance by a patient seeking advice, may be checked or supplemented by looking up these relatives in the register.

Registration and Subdivision of an Entire Population According to Familial Relationships.

By **E. Essen-Möller** (Lund)

In their investigation of Swedish Lapps, *Lundborg* and *Wahlund* (1932) worked with written family cards, assigning to every set of parents-and-children a number of its own. Reference was made, in both directions, between the card in which a person appeared as a child and the card in which he appeared as married. This system of cross-references was extended to several generations and used for tracing the descent of the person concerned.

This idea was now modified. Thus, to increase the flexibility of the system, it was preferred to use *individual cards* instead of family cards. The number indicating the particular family is of course introduced into the respective cards of all its members, however in a different space according to the position within the family. Thus while each of the parents gets this common number punched in a certain space A of their cards, the children will get it punched in another space, B. In the children's cards space A is reserved for the number assigned to their own marriages. Correspondingly, in the father's own card space B is reserved for the number assigned to his own sibship, and in the mother's own card space B is similarly reserved for the number assigned to her own sibship.

Let us from now on always speak of the *card-holder* as the starting point in every particular card. Then, to repeat, *Space B* always refers to the card holder's own sibship (full siblings) or, in other words, to *the family founded by the card-holder's parents*. Since the card-holder and his siblings have an identical number in this space of their respective cards, each of them gets an individual index attached to this common number. *Hereby any particular card-holder is unambiguously defined in space B.*

Space A contains the number assigned to *the family founded by the particular card-holder himself* (herself). (In the case of having married twice, he will get two separate cards with each a different number in space A. Illegitimate connections with resultant offspring will be treated as marriages).

Two more numbers are added, in spaces C and D respectively. The number in *space C* is concerned with the sibship to which belonged the

father of the card-holder when he was a child, that is, *the family founded by the card-holder's paternal grandparents*. Since the father and his siblings have all an identical number in space C, each of them gets an individual index attached. – Similarly, the number in *space D* denotes the sibship to which the mother of the card-holder belonged when she was a child, that is, *the family founded by the card-holder's maternal grandparents*. Also here is an index attached, thus the father and the mother of the card-holder are unambiguously defined in spaces C and D respectively. – By adding four more spaces, the principle might be extended to the families founded by the great-grandparents, and so on.

As will be concluded from this description, the same numbers will re-appear in different relatives of a certain card-holder, but they will wander from one space to another in different generations.*

This enables us to trace the relatives of a given person. If, as in Table 1 (slightly modified from *Essen-Möller*, Kungl. Fysiogr. Sällsk. Förhandl. Lund, 24, 7, 1954), the four numbers of the card-holder be called a, b, c, and d respectively, one will easily see how to proceed. For instance, the card-holder's siblings will be found by sorting out the number b in space B, but if one sorts the same number b in space A one will instead get the card-holder's parents. Similarly, by sorting out the number b in space C one will have the children of the card-holder's brothers, and b in space D will give the children of his sisters. Again, sorting the number a in different spaces will give the card-holder's husband or wife, his children and his grandchildren; and so forth.

The interesting thing might however be, not to start from a given person to search for some relatives of his, but to start, so to speak, *from all persons simultaneously* and see how they belong together by circles of siblings, circles of cousins, pairs of mates, and other *circles of equi-consanguinity*. Such a grouping might be performed by bringing, machinally of course, all individual cards of the entire population into *order of sequence according to their number in a distinct space*. For instance, when brought into order of sequence with regard to the number in space B, all cards carrying an identical number will appear adjoined, and every such cluster of cards will comprise a circle of siblings. (For other groupings, see the paper of 1954.)

Some kinds of groupings will involve a *matching* of the sequences of

* At the occasion of the congress, M. le Docteur Jean Sutter, of the Institut national des Etudes Démographiques, Paris, told me of his own "Méthode mécanographique pour établir la généalogie d'une population." This method was later published in *Population* 11, 507, 1956.

Table 1. Tracing the Relatives of a Propositus

Relationship	Family founded by			
	Card-holder Space A	Card-holder's Parents Space B	Card-holder's Paternal Grand-Parents Space C	Card-holder's Maternal Grand-Parents Space D
Card-holder	a	b	c _x	d _y
Husband or wife	a			
Children		a		
Grandchildren				
Children of sons			a	
Children of daughters				a
Parents	b			
Siblings		b		
Nephews and Nieces				
Children of brothers			b	
Children of sisters				b
Grand-parents				
Paternal	c			
Maternal	d			
Uncles and aunts				
Paternal		c		
Maternal		d		
Half-siblings				
Paternal		not b	c _x	
Maternal		not b		d _y
Cousins				
Paternal			c and/or c except c _x	c
Maternal			d and/or d except d _y	d

two or more spaces. It may then be convenient to work with two identical sets of cards, to sort them into order of sequence each of a different space and then compare them. Should the size of the population be considerable, even the procedure of matching might conveniently be performed by special machines.

Should, however, the size of the population be only moderate, there is no need for duplicate cards. Instead, the unique set of cards is brought into order of sequence first in space A, and is then machinally *tabulated* in this order. Thereupon, the same cards are re-arranged so as to give the order of sequence in space B, and a second list is tabulated. This procedure is repeated also for space C and space D. – This method has the advantage

Table 2. Sections from two tabulated lists

Sex	Age	A	B	C	D	Sex	Age	A	B	C	D
9	40	3045	96573	75891	55171	8	34	3045	07002	65491	75881
9	30		96575	75891	55171	9	28		16262	86162	75871
8	42		96572	75891	55171	8	17		16264	86162	75871
9	15		26324	75861	96471	9	36	4000	10071	81921	75862 - 126
8	20		26323	75861	96471	9	24		16202	75821	75811
8	22		26322	75861	96471	9	26	4044	16201	75821	75811
9	24		26321	75861	96471	9	30		06774	70811	75801
9	43		06901	75851	55151	9	35		06772	70811	75801
9	31		06865	75841	75941	9	37		06771	70811	75801
9	27		06866	75841	75941	9	35	3020	06743	65451	75771
9	28		06854	75831	86111	9	36		06132	72091	75774
8	38	3666	06852	75831	86111	9	34		96253	55121	75761
9	40	3504	06851	75831	86111	9	47	3627	96252	55121	75761
9	24		16202	75821	75811	8	39	3057	00442	72311	75732 - 128
9	26	4044	16201	75821	75811	8	29	3555	15542	75383	75711
9	37	3033	00391	75736	92421	8	09		15033	75651	75663
8	16		15992	75731	80012	9	13		15032	75651	75663
8	26	4573	15991	75731	80012	9	27	4562	15031	75651	75663
9	36	4569	15971	75701	71113	8	36	3603	15891	74711	75631
9	34	4568	15972	75701	71113	9	45	3621	96181	62321	75601

of providing, the four lists once prepared, a permanent basis for various and repeated comparison between spaces without any further sorting.

This will be demonstrated by sections from two such lists (Table 2), the left of which arranged according to space C (father's siblings) and the right one according to space D (mother's siblings). It will be remembered that the four numbers belonging to one and the same individual always appear together on the same line, only the lines are arranged in a different sequence in every list. One will easily see, when neglecting the indexes, that the numbers of the two respective spaces are running according to order of sequence. By following them simultaneously, one will then find instances (126, 128) in which the father of a certain card-holder has the same number as the mother of another card-holder, which indicates of course that the two card-holders have a pair of grandparents in common and thus are first cousins. There are also instance (127, 128) of two fathers being brothers or of two mothers being sisters, as indicated by their carrying an identical number but a different index within the same space, and so in these instances, too, the respective card-holders must be cousins. (When also the index is identical, it goes about siblings or half-siblings.)

A South Swedish rural population of 2550 inhabitants was investigated.

Table 3 indicates how many inhabitants had at least one relative of a certain degree, for instance, a sibling, a parent, a child and so on. The figures are preliminary, and some of them should even, as indicated by a sign, be corrected for the case the same inhabitant is partaking in two relationships of equal degree, for instance, in a paternal as well as a maternal cousinship. Probably this reduction will amount, for cousins, to 10-15 per cent. On the whole, there are 271 cousinships, and there are 443 sibships consisting of two members or more, and 1363 with a single member.

Table 3. Out of 2550 inhabitants, the following are with or without a relative in this same population (preliminary figures)

category of relatives	with	without	without down to and including
siblings	1187	1363	1363
parents	1195	1355	1064
children	1016	1534	390
half-siblings	126	2424	382
grand-parents . . .	390—	2160+	366
grand-children . . .	230	2320	358
uncles, aunts . . .	594—	1956+	354
nephews, nieces . .	383	2167	354
first cousins	984—	1566+	285

The table also shows the number of inhabitants having at present within this population no relatives closer than down to a certain degree, for instance, neither siblings nor parents nor children. Thus it is seen that the number of inhabitants who have no relatives as close as cousins or closer is only 285 (preliminary figure).

These figures may serve as an objective measurement of the amount of consanguinity existing within that particular population, while measuring in terms of frequency of marriages between first cousins is easily biased by social rules and customs. In this population, marriages between first cousins amount to 6 or 7 per thousand.

Beyond measuring the amount of consanguinity in a given population, the method might be useful for the study of familial association of pathologic and normal conditions, including demographic qualities such as age at marriage, age at death, migration, and similar. An experiment might be made of introducing family numbers to official population registers of a somewhat larger area.

J. Sutter (Paris): La connaissance de la dissémination des maladies génétiques dans une population, est étroitement liée au problème de leur enregistrement légal. Si certains pays, comme le Danemark, sont arrivés sur ce plan à un haut degré de perfection, il est loin d'en être de même dans la plupart des autres nations. Si nous prenons l'exemple de la France, on peut constater qu'il y a peu de chances d'arriver à obtenir l'obligation de l'enregistrement des maladies génétiques. Si l'on songe qu'il a fallu trente ans d'effort, pour que le parlement se décide à rendre obligatoire la déclaration d'une maladie sociale aussi grave que la syphilis, on peut même prévoir que les maladies ayant un caractère familial échapperont toujours à un enregistrement efficace.

Est-ce à dire qu'on puisse, dans ce type de pays, se désintéresser des problèmes soulevés par l'existence des maladies génétiques et par leur extension dans la population? Certainement non; mais l'orientation et l'organisation des recherches doivent s'y faire sur un plan différent. Abandonnant la voie du recensement simple, ou de l'enregistrement automatique, on peut entreprendre de rassembler des faits génétiques sur une large échelle, en utilisant l'ensemble des organismes d'assistance sociale. Dans les sociétés possédant une structure socialiste, comme on en rencontre de plus en plus dans les pays d'Occident, on peut concevoir que la collaboration des nombreux organismes officiels s'occupant de la population peut permettre des investigations très approfondies dans les champs de la génétique humaine. Nous rapporterons ici un exemple qui expliquera, mieux que des vues théoriques, ce qu'on peut obtenir dans cette voie.

L'Institut national d'études démographiques, qui constitue en France l'un des organismes techniques du *Ministère de la Santé et de la population*, s'est proposé d'étudier ce que coûtait à la Santé publique les familles qui se caractérisaient par l'existence d'une mutation bien déterminée, en l'occurrence l'absence de l'une ou des deux incisives latérales supérieures. Si comme la clinique l'observe, les familles mutantes présentent plus de cas de mortalité et des maladies plus fréquentes que les autres, elles doivent causer à la communauté des dépenses relativement élevées. Ce sont donc les frais dus à cette mutation qu'on a décidé d'évaluer en enquêtant sur un département entier (240 000 habitants).

Tous les organismes administratifs ou d'assistance participent à cette recherche. Le *ministère de l'Education nationale*, par ses services de *l'Hygiène scolaire et universitaire*, a détecté dans les écoles tous les enfants présentant

l'anomalie. Les *Caisses d'allocations familiales*, la *Mutualité agricole*, les *Assurances Sociales agricoles*, la *Sécurité Sociale*, ont fourni tous les renseignements portant sur les dépenses sanitaires, à la fois du groupe des familles mutantes et d'un groupe de familles, de niveau social analogue, pris comme contrôle.

L'*Institut national de la Statistique et des Etudes économiques*, qui s'occupe en France des recensements, a fourni des données démographiques inédites relatives aux habitants du département intéressé par l'enquête. Les autorités ecclésiastiques ont fourni les chiffres des mariages consanguins pour les années intéressées. Enfin, les médecins appartenant au groupe de la médecine rurale se sont mis à la disposition des enquêteurs, en cas de nécessité, pour tout renseignement complémentaire.

Voici donc un exemple où l'on a pu mener de pair, grâce à la collaboration d'un grand nombre d'organismes officiels, la détection et l'étude d'une mutation puis l'estimation du dommage qu'elle crée à la société. L'analyse des résultats est, d'autre part, rendue excellente par la connaissance précise de l'état démographique de la population intéressée. Pour souligner l'intérêt purement scientifique d'une recherche de ce type, signalons qu'elle a permis de détecter 305 enfants porteurs d'une anomalie des incisives latérales supérieures. C'est là un excellent matériel si l'on songe que Miss *Burks*, pour étudier le linkage existant vraisemblablement entre la couleur des cheveux et cette anomalie, ne disposait que de trente familles.

En terminant, je me permettrai de faire une remarque plus personnelle à propos de ce congrès. Les spécialistes des questions de population ont été frappés de voir le nombre élevé des problèmes d'ordre démographique soulevés par les communications faites dans les diverses sections. Il est apparu qu'il existe trop peu d'échanges entre les spécialistes de la génétique médicale et ceux de la génétique démographique. Si ce regrettable état de chose tient aux difficultés de l'enseignement scientifique, il est certainement imputable aussi à des difficultés d'ordre bibliographique. La diffusion des travaux de génétique humaine est loin d'être satisfaisante. Le moment est sans doute venu de créer une revue bibliographique intéressant toutes les branches de la génétique humaine. La démographie a rencontré des difficultés analogues au cours de son développement et la création, en 1945, d'un *Population Index*, sous les auspices d'un groupe de chercheurs de l'Université de Princeton, a rendu un service inappréciable à cette science. Il est à prévoir qu'un *Genetics Index*, édité sur des bases analogues et qui fournirait périodiquement une bibliographie de toutes les spécialités, donnerait un nouvel essor aux recherches qui nous tiennent à cœur, en leur assurant peu à peu l'unité qui leur fait encore défaut.

Introducing a "Personal Health Card"

By **M. Milani-Comparetti** (Rome)

Following the report, last Thursday, by *Professor Gedda*, a number of people have been asking for copies and information about this which we call, in Italian, "*Carta Sanitaria*". As we do not have here enough copies to circulate them among all the members of this Congress, we thought it best, with the kind and prompt cooperation of the Congress Committee, to say a few words about it here.

I will start by pointing out that what we have here is only a sort of proof, a sample, intended to exemplify how we believe that genetics can be of real, direct service to the individual and to his doctor. We think, in fact, that even if it is only through chance, it is nevertheless quite right that we talk about this in the course of this session dealing with social application of human genetics. It is quite widely felt that a higher degree of reciprocity must be reached between genetics and other branches of medicine, and between geneticists and medical doctors in general, whether they be general practitioners or specialists. At present it very generally happens that, whenever some genetical research is deemed advisable concerning an individual, whether it be for a diagnosis, for treatment, for counseling or for general research convenience, the entire burden of drawing up the genetical picture of that individual rests with one doctor, and on the other hand the result of his effort is generally bound to be of service to him alone. This accounts, evidently, for a number of troubles: first, the individual doctor will probably avoid as far as possible any such research, thereby renouncing the assistance his work and his patient might receive from genetical information. Second, if he should decide to get the patient's genetical picture, this would require each time a lot of effort and time. Third, the information thus eventually gathered would certainly be an asset for the doctor's records, but it hardly could be of service to the patient elsewhere.

If we thought that genetical data were only useful for our own laboratories, institutes and, perhaps, congresses, we would have no reason to worry. But if we feel, as I think we do, that our studies are intended to

improve the welfare, the treatment, the care of individuals as well as populations, then we must try to make what I would call the individual's genetic picture a normal tool for the entire medical profession.

For this purpose we suggest that the "tool" might take the form of this . . . card. As I pointed out, I do not know yet how best to identify it. I will leave the matter to the committees on nomenclature. In the meantime I will call it "personal health card".

This card ought to accompany the individual throughout his contacts with the medical profession, and should include as a matter of course all those items of information that are, or will be, considered as genetically relevant. In order to be clear I will rapidly go through the pages of our card as we have tentatively arranged them.

You will notice that we start with this series of special markers, which are identified in the second page: they are meant to indicate at first glance some fundamental data concerning the subject: such as his being born to consanguineous parents or being a twin. Then pages one and two contain the basic information on the patient himself, and are filled in by whoever originates the card. Pages 3 to 8 are meant for additions to the individual's medical history, always listing the name of the doctor who brought the card up to date. The red pages contain relevant information on the parents and other ascendants, while the green ones are intended for whatever collaterals may be deemed relevant. (Possibly all!) Then, in the yellow pages, we report on the wife (or husband, of course) and on all the descendants. Finally, we have a "fundamental" family tree, which very often, of course, may not be sufficient, but which can serve at the same time as a start and as a reminder.

I just said that the basic information is listed in the card by whoever originates it. This may be a difficult problem. Personally, I would be in favor of asking the obstetrician to originate the card, both because the individual's life starts right then and because he is the only one to have available all the very important information concerning conditions at birth. But the obstetrician may not always be there, and no pediatrician in the following years. In this case we ought at least to advocate that the "personal health card", if not made before, should be originated when the individual first goes to school. It is at that point, in fact, that he is bound to come in contact with society, and at this point therefore we can be sure that he is equipped with his card.

Whenever there is one, of course, the ideal man to take charge of this card would be the famous "family doctor". And in this case our card may very well become a practical means of co-operation between him and any

specialists, making normally available to the former the latter's knowledge, and vice versa.

I realize very well the misgivings and opposition such a plan may arouse. Many people are apt to think that genetics are not as important as all that and that we are trying to make a mountain out of a molehill. Others will simply dismiss the plan as impossible. Others will shout at bureaucracy, at socialism, that we already have enough forms and cards and passports to fill...

Some of this may be true. Perhaps our plan will reveal itself as utterly impossible. But perhaps it can be tested, certainly it would have to be improved, and finally it may come to make a tool out of a gadget. If any of you feel that something could and should be done along these or similar lines, we ask for their advice and possibly co-operation.

Reed, S. C.: Acta genet. 7, 473-480, 1957

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COUNSELING IN MEDICAL GENETICS

By S. C. REED

There is an old story, many times retold, which has significance for us. The story goes that, on hearing about Darwin's theory of evolution, a lady cried: "Descended from the apes! My dear, we will hope that it is not true. But if it is, let us pray that it may not become generally known." To her, it was terribly degrading to be related, however distantly, to an ape. Eventually the news became generally known, and most people reconciled to their strange relatives. However, reconciliation is not quite the same as love. We may admit our relationship to a now extinct hairy primate but we do not enjoy doing so. We are emotional rather than objective about our relatives. We do not wish to identify ourselves with pre-human forms having limited capacities.

Many people point with pride to their descent from one or more of the

passengers who came to America on the Mayflower. My own ancestry contains a sprinkling of those courageous souls who opened up the New World. We cheerfully accept the implication that all our good traits were inherited directly from a few of those now famous progenitors. We ignore the other four or five thousand ancestors of that time even though each made an equal contribution to our heredity. Some of the now forgotten ancestors were probably widely known in those days as pirates or witches. This tendency to identify ourselves with the famous and to reject the undesirables from our ancestry may give rise to a superiority complex, which in this case rests upon what could be called the "Mayflower Myth".

The point which I am making is this: people accept the concept of heredity for traits which they admire and reject it for the traits they shrink from.

Medical genetics is usually concerned with deleterious traits and many of them are actually lethals. The counselor's clients do *not* wish to learn that their problems have a genetic basis. They want to be told that albinism is *not* hereditary, and that their albino child is just an exaggerated Scandinavian! If three consecutive generations of congenital cataract are present in a family, the clients will favor the less probable interpretation of recessive heredity rather than accept the more likely hypothesis of a dominant genetic mechanism. This is because with recessive heredity the chances are smaller that the trait would reappear in their children. Many of the parents of the mentally retarded reject the concept of heredity because to them this implies a Jukes or Kallikak kind of family which naturally no one would wish to acknowledge.

If the sincere client fundamentally does not wish to accept the concept of heredity for himself, though he may be willing to accept it for others, what effect does this attitude have upon the counselor and the counseling? Naturally the counselor wants to make his clients happy even though the counseling is always gratis. Consequently, he would *like* to find an environmental accident, infection, or other non-genetic cause for the appearance of the trait in question. He is likely to over-rate the probability of an environmental etiology and under-rate that of heredity in order that the conference have a happy ending. However, if the trait is dependent upon a Mendelian dominant or recessive gene for its expression the counselor will have to listen to his conscience and tell the truth; not brutally, but in an "educational" way. Otherwise the counselor will find himself in trouble later on.

The counselor cannot afford to over-rate the influence of environmental factors such as German Measles and automobile accidents, because the lady

involved cannot be expected to have a second case of measles at the right time to explain the second abnormal child. As many physicians have found to their surprise and regret, lightning *does* strike twice in the same place and in the same way quite frequently. If the trait is a Mendelian one, and the chances of a repetition of the trait are one-half or one-fourth for each subsequent child, there is a reasonable probability that the clients will be back to see you after having produced a second affected child.

Today's young people have accepted very literally the philosophy that every couple should have a family. If the couple is infertile, then they should attempt to have their reproduction stimulated at the fertility clinic. The only limitations to the philosophy are that the children be spaced according to the medical and economic situation, and that they be wanted. Otherwise the sky is the limit, and the American population is growing with joyous planned abandon.

The present compulsion to produce a family makes the lot of the genetic counselor rather difficult. No matter how catastrophic the genetic situation may be, the young couple feels compelled to complete their family. Let me illustrate with a recent counseling case. The wife has been totally blind for several years, her eyes having been enucleated because of glaucoma. Her sister is also blind for the same reason. The husband has very poor vision because of congenital cataracts. His father has the same difficulty. The couple have one child, a baby representing the third generation of cataracts, and with a poor prognosis for vision. Statistically speaking, the couple have at best an even chance at each conception of initiating a child with normal vision. The husband and wife were aware that both eye defects were genetic and wanted to know their chances of producing normal children.

It is only rarely that the genetic counseling goes beyond educating the couple so that they understand what the chances are of a repetition of the abnormality in subsequent children. However, in the above case it seemed useful to point out to the couple that they faced a dilemma even if their subsequent children did have normal vision. It has been observed that in cases where a handicapped couple with one or more handicapped children have a normal child, that it is likely to feel out of place and have psychological problems contingent upon its failure to correspond to the other members of the family. This was a new concept to them. It will be interesting to observe this family in the future.

The question of how far the genetic counselor should go in making suggestions is worth consideration. In the United States there are a dozen heredity clinics and in most of them the policy is relatively uniform. The

counselor does his best to explain the genetic and environmental factors involved in the situation with the expectation that the couple will then make an appropriate decision as to their subsequent reproduction. Definite advice as to future decisions is not given by the counselor. He cannot place himself in the clients' position and therefore cannot make the decision for the couple. At the time of the conference the husband and wife have not stabilized their thinking and do not know what they will decide eventually.

It is more or less "fashionable" at present to deny the role of heredity, though the biologist knows full well that all traits, good and bad, result from the interaction of heredity and environment. The open questions concern when and how the genetic and environmental factors function. Many of the people who verbally deny the concept of heredity, in actuality are found to be more pessimistic about their heredity than the facts require. Some actually think that having had one affected child, *all* their subsequent children will be affected. Very rarely, such is the case, though too seldom to be of concern to the average couple. In many instances these apprehensive couples have been re-contacted several years after the conference. Generally it seems to have been helpful in reducing their worries, and thus has encouraged them to have larger families they had previously thought wise. An example follows:

A young minister and his wife had refrained from having children because the minister's brother had convulsive seizures and they were in doubt as to the magnitude of the chances they would be taking if they had children. It was requested that both husband and wife have electroencephalographs taken. This was done and the wife's brain potentials appeared normal but the impression obtained by the physician from reading the husband's E.E.G. was one of dysrhythmia indicative of petit mal seizures. It was explained that half of their children should display the dysrhythmia but, like their father, most of them would not have seizures—even though the dysrhythmia was present. At worst not more than one in eight of their children would be expected to develop seizures. Contact was re-established five years later and it was breath-taking to discover that the minister was not only serving three rural churches simultaneously but had fathered four children in the five years!

Unfortunately the world is not entirely without its shadows, and in some cases the genetic counselor cannot tell the couple that there is no chance of a repetition of a particular abnormality in a subsequent child even though he would like to do so very much. In some cases the decision has been made before the person appeared for counseling. An illustration of this situation was presented by a 24-year-old mother who came to the

Dight Institute after several years of trouble due to cystic fibrosis of the pancreas in two of her four children. One of the sick children had died but the other child was still living at the age of 6, though half of his life had been spent in hospitals. The expenses each year had been much greater than their income and they had lost their automobile, their house and part of their ambition. The more recent expenses were borne by "county papers". The county had a legal right to any property they might accumulate until their debts to it were paid. Since the mother had already had two fibrotic children, she was no longer in the market for the "lightning never strikes twice in the same place" myth. She had already made her decision that her two normal children and the two sick ones were all that she was having. She had come to the Dight Institute merely to check on what she had learned elsewhere, that the chance of a repetition was still 1 in 4 for this disease at each subsequent pregnancy. She wanted to be sure of this before going ahead with a sterilization procedure.

There are other serious and heart-rending diseases which handicap children and force parents to take action that otherwise they might not consider proper. Two such afflictions are the two sex-linked traits for hemophilia and pseudohypertrophic muscular dystrophy. The counselor does not "like" sex-linked traits because with them the responsibility rests entirely upon the mother; it is probably better for the responsibility to be shared by both parents.

An older couple had produced five boys, three of whom had developed the sex-linked type of muscular dystrophy and were incapacitated in order of their ages. The three sick boys were being cared for by the mother but were a heavy burden for her. She was greatly upset and disturbed to discover that she was pregnant at the end of her reproductive life. The couple had asked for a therapeutic abortion as a way out of an intolerable situation. As in the previous example the couple had decided what they wished to do and were at the Dight Institute to make sure that they had their genetics straight.

Some families have to contend with more than one kind of anomaly. Their reactions to the traits which have appeared in their children are of considerable interest as demonstrated by the summary of a very recent conference. The husband has a harelip and cleft palate with reasonably good repair. The first child was premature, had a harelip, and died. The second and third children were normal. The fourth child was hydrocephalic and had to be delivered by Caesarian section. Because of the fact that the mother had influenza during early pregnancy it is possible that the hydrocephaly was due to meningitis and not genetic in the strict sense. Without

any genetic consultation the couple had requested donor insemination and their obstetrician had made two unsuccessful attempts. At that point they heard of the Dight Institute and came for consultation.

The couple did not fear the repetition of harelip and cleft palate as they had faith in the ability of the plastic surgeon to repair the damage. But they were perturbed about the possibility of a repetition of the hydrocephaly, or spina bifida, even though it seemed likely that their affected child was the victim of an infection. Even if it were a result of genetic damage, the chance of repetition is only about three per cent so they had ninety-seven chances out of one hundred of a normal child at the next pregnancy, for this particular anomaly. The chances of a repetition of harelip and cleft palate are from ten to fifteen per cent with confidence that it is genetic, because of its previous appearance in both the father and the first child.

The interesting features of the above case are that the mother is determined to have five living children which means three more pregnancies, all of which, to them, would be fraught with danger. They were not concerned about the moderately large chance of a repetition of the less serious anomaly, harelip and cleft palate, but were disturbed by the very small chance of a serious defect of the central nervous system. The conference seems to have been helpful in removing some of their unnecessary fears about the repetition of hydrocephaly in a subsequent child. It also encouraged them to augment their family without outside assistance. Donor insemination would be useful where the husband is actually sterile, and in some genetic situations, but would seem to be of questionable value in this particular situation, because of the possibility of incomplete acceptance by the husband of the children so produced.

A final point warrants consideration. This is the matter of imparting negatively charged information to the client. It is good medical practice *not* to tell the patient anything that will cause anxiety and thus be damaging to him. This is a good common sense rule, if applied thoughtfully. However, the withholding of certain information may sometimes result in disaster. It would seem proper to apply insurance principles of producing a little apprehension in every client in order to protect a small percentage of these clients from serious mental distress at a later date. A case in point can be demonstrated by genetic counseling for Mongolism.

It is well known that the frequency of Mongoloid children goes up with mothers over 35 years of age at a rapid rate. One third of the affected children are born to mothers over 40 years of age. As the Mongoloid child is often the last child the family had intended to have, no subsequent

children will be produced and consequently few families demonstrate a repetition of the anomaly. Therefore, it might seem wisest if all mothers producing a Mongoloid child were assured that there is no chance of a repetition of the defect. This would be *positively* charged information which the family would be happy to obtain. However, for the young mother who has produced a Mongoloid child this information would be false. There is a small but real chance that this mother might produce a second or even a third Mongoloid child. Having been educated to believe that this could not happen to her, the shock will be severe and much more distressing than if she had taken a calculated risk and lost. The following family history demonstrates both sides of the picture.

A 23-year-old mother gave birth to a Mongoloid boy, then to a normal girl and at the age of 29 to a Mongoloid girl. All three pregnancies were completely uneventful and before the second and third children were born the mother was assured by two physicians that there was no danger of a second Mongoloid child and she had come to believe it. Without warning, the second abnormal child was presented to the mother, with resulting psychological trauma, as she made the diagnosis herself. It took the mother some months to recover her mental equilibrium. At this stage the couple appeared for counseling.

Upon examination of the hands of the couple, the husband showed a striking "simian crease" of the left hand and a less pronounced demonstration of it on the right hand. The wife's hands were normal. The crease on the husband's hands suggested that there was something more than an environmental insult involved in the etiology of their affected children. The couple were warned that there was a small but real chance that they might yet produce a third Mongoloid child. They were willing to accept this possibility and were relieved to find that the probability of its happening was small. Being prepared for the worst, the couple have since produced two normal children and have a sense of elation from having won in their latest encounter with the biological lottery.

In conclusion, a definition of the subject of counseling in medical genetics might be useful. This name is not entirely appropriate for the subject but it is firmly established, in the United States of America. In Denmark, where large scale genetic counseling originated, the name for it is "Genetic Hygiene". This term would not be entirely suitable in the U.S.A. where the word hygiene is usually associated with strong soaps, tooth pastes and other products employed in personal sanitation.

Counseling in medical genetics is not counseling in the legal sense of recommending or advising because the clients are not given directions as

to what they should do. It is not particularly medical as the healing aspects are slight, if any, and the diagnoses are presented to the counselor and not made by him. The diagnoses may be made by an alphabetical galaxy of physicians and specialists ranging from A for the anthropologist to Z for the zoologist. The subject matter is based on the science of genetics but empiric risk predictions must often be made concerning traits where environmental variables are of great importance.

It is easy to state what counseling in medical genetics is not. It is more difficult to say what it is. As a result of some experience in the field it is my conclusion that counseling in medical genetics is a type of social work carried out by the geneticist or family physician. It is a helping process which should contribute to the unity and development of the family. It is intended to develop intellectual security and peace of mind for each couple, and to help them gain the happiness to which we all aspire.

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THE PLACE OF HUMAN GENETICS IN THE TEACHING OF PUBLIC HEALTH AND SOCIAL MEDICINE

By C. GORDON

To some it may seem strange that a paper of this title should be presented at a congress of professional geneticists at which the main communications are overwhelmingly connected with current research. I do not apologise for this because, as I understand it, the purpose of our congress is the furtherance of our subject and the educational aspects are of sufficient importance to warrant some attention. Moreover, some years of teaching experience of the subject has led me to re-examine certain basic aspects of its position.

For the purpose of this examination of the place of Human Genetics in the Teaching of Public Health and Social Medicine I am making the assumption that the student is adequately grounded in Human Genetics in relation to Clinical Medicine. It is, however, unfortunate that this assumption is not justified. Though human genetics is fundamental to the study of aetiology, broadly speaking it can be said that the student comes to his clinical years with an orientation that is derived from the studies of the relation of gene to chromosome rather than from appreciation of the variability that would be disclosed by inbreeding free living *Drosophila* populations. To supplement in part, a picture of genetics derived substantially from linkage studies in *Drosophila melanogaster* he should also have an account of eyeless and abnormal abdomen dealing with the changes in exhibition with age of culture. In these we have a steady change of exhibition with age of culture. To complete the story, perhaps he might also be told about the U-shaped curve of exhibition of Antennaless which I discovered when working on wild populations. In this instance the exhibition is highest in the first emergences, falls until the fourth or fifth day and then rises again. This was worked on further by Sang and myself [2], showing that the antennae would grow if there were added the appropriate B vitamins. Moreover, we also showed that there were modifying genes affecting the exhibition. It is this complex picture of main gene, modifying gene and environment that is needed before entering into the special difficulties of human genetics, quite apart from some introduction to quantitative genetics. It is my considered opinion that it would be preferable to omit genetics from the training of the medical student than to continue with the over-simplified picture from genes appropriate to linkage studies. Certainly for those who are to initiate genetic counselling or even to interpret genetic counselling, a simplified guide that avoids the full complexities is dangerous.

Public Health and Social Medicine is most frequently studied late in the undergraduate medical curriculum or as part of post-graduate training for those who administer the public health and medico-social services. One of the justifications for teaching genetics is that it is an aid to early ascertainment for such conditions as deaf-mutism, rheumatic heart disease or schizophrenia. To my mind this is clearly specious for it does not matter whether a condition is genetic, environmental or a mixture of both. All that is needed is a knowledge of the facts of what has been termed "empirical hereditary prognosis". The technical problems of ascertainment lie solely in the field of administration. A more serious example of the impact of genetics is in the schemes for foster-parents or adoption. A substantial number of people concerned with placing children set out to match the

parents and the child in regard to intelligence and sometimes even in regard to personality traits. These people are thus assuming, sometimes explicitly, that intelligence and personality are characters where genetic transmission is clear and where there is a low plasticity in response to the environment.

Another type of situation with which Public Health administrators are faced even at the local level is the effect of modern therapeutic measures upon the expectation of life of handicapped groups, e.g. mongolism and other types of mental defect. This, illogical though it may be, has been associated with the other question first raised by *Pearson* of the dysgenic effects of the reduction of mortality. The increased incidence in the community of defectives in the main raises questions of how to deal with them, but this is scarcely dysgenics or eugenics which is concerned with gene frequencies. Another concern is over the so-called "Problem Families", who are a serious responsibility. Though advice and guidance for limitation of families can be based solely on the immediate situation of the physical effect upon the woman of continual child bearing and the better opportunities for the existing children, questions of genetics are raised in the form of whether or not there should be clinics for this purpose which are confused with heredity clinics? At national level there are the possible consequences of differential fertility and, even more topically, radiation hazards. These seem to me to be the topics that are relevant to Public Health and Social Medicine—more so than blood groups and the rhesus question, though there are still practitioners who do not use the nation wide serological services appropriately. Though a knowledge of the genetics of the situation could be appropriate, correct practices are not dependent on the understanding of the genetics of blood groups, as shown, in my experience, by the excellent work of health visitors (public health nurses) who have had no training in genetics whatsoever.

These topics have merely to be stated for it to become abundantly clear that they can only be covered in an extensive course at postgraduate level. As that is not possible, the question that arises is: what can reasonably be done?

At first sight one answer that occurred to me was the dogmatic presentation of conclusions, but this presented difficulties at two levels—the first was that of selection of the dogma and the second was the students acceptance of the dogma. To deal with the first of these, how would one treat the genetics of criminal traits from twin data, short of ignoring the subject completely?—an irresponsible decision since it is quoted so frequently.

To put this problem in its simplest form, I shall quote from *Stern* [4]: "One who is impressed by the role of heredity in the many similarities of

identical twins is again inclined to attribute the greater concordance in criminality of identicals as compared to non-identicals to the identity of the former's genotypes. The greater similarity in the environments of identical twins may, however, play a role in this behavioristic trait. If non-genetic chance led a twin into a criminal offence, would not the similarity of the environmental experiences of an identical twin partner often lead him to similar crimes, in contrast to a non-identical twin partner who did not share the unfortunate chance association? It is, indeed, likely that these factors are significant in some cases; but a detailed study of the twin pairs does not seem to support the environmental interpretation as *generally* valid. In many cases, the identical twin partners both became offenders at a time, after their common childhood, when they had no more contact with each other; and non-identical twin partners were often discordant, even if closely associated with each other."

Stern, it seems to me, places too little emphasis on the persistence of behaviour patterns that may be built up during childhood into adult life of twins who were together in childhood and had parted by the time that they had become criminals. My own conclusion from *Lange's* work is that both heredity and environment play a part, not a very profound conclusion when one considers the general inter-relation of heredity and environment. The difficulty of this conclusion is that if it is presented shortly, it scarcely seems worth saying.

To do more than this, would entail devoting a much longer time than can be usually contemplated.

In contrast to *Stern* there is *Darlington* who has expended much ingenuity in trying to demonstrate complete genetic determinism—not to my satisfaction at any rate—but a very interesting feature is *Darlington's* acclaim of administrative and judicial classification as a basis for genetic studies—in contrast to the unremitting search of all other geneticists that I know of for more clearly defined biological entities. Lest it should be thought that I am misrepresenting *Darlington* [1], I shall quote the relevant passage *in extenso*: "Among all social studies with twins the study of criminal twins is most fruitful for several reasons. Conviction, or lack of conviction, for crime provides a thorough, and impartial, as well as economical means of testing the similarities and differences between individual members of society: thorough because the law has exacting standards, impartial because it makes no scientific assumptions and has no scientific theory in applying these standards and arriving at its judgment. It is emotional and traditional rather than analytical or experimental. Conviction of course to some extent depends on luck; accidental other-level interference comes in. But the study of numbers can allow for this vagary."

It is important to note that a study is impartial because it involves no scientific assumptions and has no scientific theory in applying these standards and arriving at its judgment. The full meaning of the statement will be clearer if it is restated positively rather than with double negatives, as follows: "Starting with clear and unambiguous premises, which are accepted either *a priori* or from observations, and developing a scientific theory we are bound to arrive at a conclusion that is biased."

Similar problems of steering between the Scylla of banality and the Charybdis of oversophistication arise in considering the rate of elimination of genes. In general, vivid concise presentation can deteriorate into a partisan statement in this delicate area where scientifically validated facts jostle with value judgments. To put forward with equal emphasis both the extreme eugenic and opposite viewpoints would be a very different task, but may in the end be the only way of achieving perspective. But it would be an extremely time consuming exercise.

So far I have outlined the problems of dealing with Human Genetics from what might be called the practical or vocational aspects. It is now necessary to examine how the subjects would fit in if approached from a more fundamental standpoint. To begin with, therefore, it will be necessary to choose or emphasize one from among several, not necessarily mutually exclusive, definitions of Social Medicine. I shall take that of my old chief Prof. Crew, namely "Social Medicine is the Medicine of groups and categories in the community." This becomes very largely the development of the theme "Environment, physical and social, as cause", and to complete the picture Human Genetics forms a part in the theme "Individual as cause". In effect, this is a restatement of the Nature-Nurture nexus.

I come now to the student's acceptance of the dogma.

In what follows I am proposing to be somewhat speculative and to voice misgivings, some of which on fuller investigation may prove to be groundless. I have personally been perplexed by the large number of instances in examinations where the student has failed to state the correct inter-relation of heredity and environment. This is of course not surprising in any examination; what has been puzzling me is that a genetic interpretation is very common, while the environmental interpretation is rare. To illustrate the point I shall describe the sort of situation that arises in the consideration of tuberculosis. In Great Britain a common way of describing the effects of living conditions upon health has been by means of the Registrar General's five Social Classes, which are in fact aggregates of detailed occupational groups: Social Class I referring to higher professional and executive classes; Social Class III to skilled manual and clerical

workers, and Social Class V to the unskilled and labourers. Social Classes II and IV are the intermediate groups. In tuberculosis the mortality increases as we pass from Social Class I to Social Class V and this is regarded as evidence that living conditions are an important contributory factor. On the other hand twin data are used to demonstrate the existence, or at the lowest, the probability of a genetic susceptibility. It is, of course, a breach of logic to infer that Social Class is genetic and that the frequencies of the gene or genes for susceptibility to tuberculosis increase as we pass from Social Class I to Social Class V, but this is a frequent answer.

The explanation for this kind of response might be distressingly simple such as the belief, that since the subject is called genetics, the examiner wishes a reply supporting genetic causation.

The question of the place, therefore, of Human Genetics cannot be answered in terms of practical application or of theoretical considerations limited to the subject itself. It must also take account of the cultural overlay of the people being taught.

The impact of theories, supposedly based on biological principles, on social policy, education and "race" relations, has often been discussed, and though the book is now some twenty-five years old, I know of no better statement than that of *Hogben* in his *Genetic Principles in Medicine and Social Science* [3]. If he were writing it today I have no doubt that *Hogben* would bring his wit and erudition to bear on the search after the chimera of a culture free intelligence test, and the pricking of the bubble of the Decline of the National Intelligence [5] by the 1947 retest of Scottish school-children. But there would still be something missing. How does it come about that people of great ability and competence can differ so radically about the social implications of biological findings. It is not enough to say, even if it can be proved, that attitudes are influenced by social class and by the political relations associated with ethnographic groups in man. The undemocratic eugenics of the past may perhaps be thought of as the genetic expression of the culture of these particular groups.

For my part, I admit that I believe that much writing is biased by class and race prejudice—the national and international sides of the same coin. But I should very much like to be able to establish or disprove this assumption by scientific investigation. And if important leading scientists may be so influenced, how widespread may these attitudes be in the community or in groups in the community? Until this is known the problem of what to teach and how to teach it can only at the best be intelligent guess work. With comparatively recent experience in Europe in mind, no one can under-rate the importance of attitudes towards race problems, for after all the theories were obviously acceptable to a large number of people,

as indeed they are still acceptable in the Union of South Africa and some Southern States of the U.S.A.

From this I have come to two main conclusions. The first is that a course in Human Genetics should deal with the problems of the cultural background of genetic concepts. Unfortunately at present this must be largely speculative and influenced by the point of view of the teacher. But if the basic assumptions and considerations are clearly stated, it is perhaps the beginning of scientific understanding. The second is that it is important that this question should be investigated. In essence it is not a genetical problem but one of social psychology or sociology. But it is a field of enquiry that geneticists should encourage and collaborate in. Such collaboration would not only be important in elucidating the subject itself but would result in a more humble approach to the problems that face social scientists than is shown by some geneticists.

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Discussion

W. S. Wildervanck (Groningen): Dr. Gordon spoke on the education of *medical* students, but I would like to stress the desirability of education in human genetics also for some other categories of students. I would like to say something about students of whom I have experience.

(1) *District Nurses*: For their examination human genetics in the Netherlands is obligatory. Human genetics is included in their course as a part of social medicine. These courses are in most cases given by a practitioner who gives them 8 hours teaching on human genetics, and I must say, the nurses are very interested!

(2) In The Netherlands at most Academics (High Schools) for gymnastics, human genetics is obligatory. In Groningen, in the second study year I give a course in human genetics one hour weekly for a whole year. I emphasize, of course, the genetics of *normal* properties, morphological as well as psychological (intellect etc.) (Of course, I don't teach them the mode of inheritance of diabetes etc.).

(3) At high schools and secondary schools something should be taught about human genetics when speaking on general genetics. My experience is that these pupils, too, are very interested.

(4) And finally—but in this category I have no personal experience—I think it is most desirable to teach *University Students in biology* something of human genetics in addition to general genetics. University teachers in biology often forget that man is a biological object too.

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New York City, U.S.A.

THE PUBLIC AND HUMAN GENETICS

By A. SCHEINFELD

A few months ago a brilliant pre-medical student, who had been planning to go into psychiatry, told me he would consider changing to human genetics as a career *if* (I quote him) “there was a substantial future in it”. He wanted my honest opinion. I told him it all depended on whether one thinks of the immediate future, or the *future* future.

In other words, looking well enough ahead, human genetics as a profession may hold tremendous possibilities. But for the present, while our science certainly has made commendable progress, the fact must be faced that in practical terms of job opportunities, financial rewards and available research funds and facilities, it still offers much less today than do many if not most other specializations.

To cite a few facts as they now apply in the United States: Only about 1 in 10 of the accredited medical colleges, and hardly 1 in 100 of all the other colleges and universities, offer as much as a single semester course in human genetics. In the entire area in and around New York City, with dozens of colleges and hundreds of thousands of students, not a single institution has a regular undergraduate course in the subject, or employs a full-time human genetics instructor, although one institution—Columbia University—does conduct a graduate seminar in the science. In the country at large there probably are no more than a dozen full-time human geneticists, and no more than two or three annual graduates in this speciality. For the most part, those active in the field are part-time workers, mainly medical men, general geneticists and some social scientists. But the great majority of American professional people who should be interested in human genetics have had little contact with it, and do little or nothing to en-

courage its teaching, research or support. Except for Denmark, the situation may not be much different in most other countries.

Why is all this so? The answer cannot be simply that "human genetics is a new science". Actually, it is more than fifty years old—as old, if not older, than many other modern specializations which have made vastly more progress. Nor can one say it is merely a branch of genetics as a whole, or biology, or medicine, for it draws on these and many other sciences and combines something of all into its own unique structure. Nor, again, can one argue that it is lacking in major public importance and interest, for it deals with the very essence of human lives and relationships. Indeed, this latter fact may hold the very explanation we seek. For it is precisely because human genetics touches the lives and beliefs of human beings so intimately that, far from having been met merely by indifference, it has incited a host of adverse reactions such as no other science has encountered. What I shall try to do in the limited time available is to sketch out some of these reactions, as I have found them in many years of writing and lecturing about human genetics, and in my personal contacts with the public and members of the professions concerned.

A primary bias, familiar to most of us, dates back to the very beginnings of our science, when it was seized upon by the early extreme eugenicists to support their theories regarding genetically superior and inferior classes, peoples, and races, and their ideas for rigidly suppressing the breeding of all those whom they considered "unfit". Unfortunately, despite their repudiation by most geneticists, as well as by leaders in the modern eugenics movement, the early eugenicist theories are still linked in many minds with the science of human genetics, and continue to engender antagonism and suspicion toward it.

Aggravating this situation has been the remarkable rise and growth of the "environmentalist" movement everywhere. This has been the age of Freud and psychoanalysis, psychology and psychosomatic medicine, with sweeping emphasis on the effects of environment and the minimizing of hereditary influences. Politically and socially, in one nation after another, there has been an assault on hereditary class structures, and everywhere once presumably "inferior" groups and peoples have burst out with unexpected strength and capacities. And throughout the world, the tremendous recent advances in health, longevity, learning and achievements, resulting solely from rapid changes in environment, have in many eyes dwarfed the importance of human genetics.

Even more, there has been a tendency in intellectual circles to regard any stress on inherited human differences as "undemocratic" and "reactionary". This attitude was heightened by the "Lysenkoist" attacks,

which misled a great many people into doubts about human genetics which still persist. At the same time, the perversion of genetic theories during the Nazi reign, and the sterilization and extermination orgies on the basis of pseudo-genetic principles, may also have increased suspicion toward the objectives of eugenics and genetics.

Another negative factor, I believe, has been the disproportionate association of our science with the pathological and abnormal. One may easily explain this by the fact that the medical profession had a big head start in compiling pathological pedigrees long before there was any science of genetics, that the large majority of our active researchers today are medical men or connected with medical institutions, and that most of the research funds have come through medical sources. Be that as it may, for the general public human genetics tends to conjure up gruesome thoughts of idiots, imbeciles, mentally-diseased and other abnormal individuals; and in families in whom these occur, it incites fear and shame. Some of this feeling arises from old notions that hereditary afflictions are punishments for sins. It may also stem from the widespread fallacy that if a condition is hereditary, nothing can be done about it except to stop those affected from having children.

At any rate, it is significant that in the present fund-raising drives and publicity campaigns in the United States to combat mental diseases and defects, heart afflictions, muscular disorders, epilepsy and other conditions, the role of heredity, where it is involved, is either ignored or played down as much as possible. So, too, the large popular magazines show an aversion to publishing articles about disease inheritance unless cures for the conditions have been reported or are in sight. Thus, widespread publicity was given to the dubious (and soon discredited) claims that feeble-mindedness could be cured by glutamic-acid treatments, or that IQs of idiots could be raised 50 points by special educational methods.

It is hardly surprising that the public is most receptive to findings which carry a hopeful note. As the best example, the "Rh" discoveries helped so enormously to win favor for human genetics because it was quickly shown how they could be applied toward saving the lives of thousands of babies yearly. Most recently, new hope for treatment of mental diseases through drugs has made psychiatrists and the public far more sympathetic to theories of inherited factors in these conditions. Of course, medical geneticists cannot and should not govern their researches with the practical applications always in mind. But they can win much more support for their work by stressing its positive aspects wherever possible.

In other areas much also can be done to overcome biases against human genetics. Psychologists, for instance, may find that in crediting or blaming

environment and early conditioning for almost everything that happens to people, they are placing an unjust and unsupportable burden of responsibility on parents and society. It is precisely in the intellectual circles, where environmentalism has had its strongest hold, that mothers are driven frantic by guilt feelings when anything goes wrong with a child. By making the public better acquainted with the role of heredity in producing individual differences, parents may be helped to recognize both the potentialities and limitations in their children, and to rear them with more wisdom and peace of mind.

Among many social scientists there has been antagonism toward bringing out facts about hereditary differences among races or ethnic groups. This, of course, is because such facts have so often been twisted to support race prejudices. What might be stressed, then, is that human genetics, far from aiding intolerance, has helped greatly to undermine many of the most harmful myths of race by proving that all human beings have a common origin; that there are no "pure" races; that genes of all kinds and qualities are distributed among all peoples; and that major racial and ethnic differences in behavior and achievement are probably due mainly to environments.

Now I should like to come back to my belief that there would be more public support for human genetics if it were not so heavily slanted toward the pathological and abnormal. I in no sense imply that there should be less activity in medical genetics, but only that there might be more research with respect to "normal" traits in which the general public and the educational and professional fields are profoundly interested. For instance, knowledge regarding the inheritance of normal facial details, stature and body form, and pigmentation of hair, eyes and skin, has been advanced little beyond what was brought out almost three decades ago. It cannot be argued that such research is scientifically unimportant, since increased knowledge about the genetics of easily identifiable and common surface traits may prove of immense value in linkage studies, in "tagging" hidden defective genes, in increasing exclusion chances in doubtful paternity cases, and in other ways.

There also has been far too little genetic study of normal mental and behavioral differences, and of genius, talents and capacities of various kinds. True, these complex traits are difficult to explore. But many of the difficulties might be overcome if human geneticists succeeded better in enlisting the interest and co-operation of psychologists, sociologists and other specialists. In fact, it is increasingly apparent that from here on human genetic research will demand more and more teamwork with scientists from many other fields.

A particularly challenging area is that of *genetic differences between human males and females*. There is mounting evidence that these differences go much deeper than was previously thought, and affect virtually every aspect of human biological make-up and functioning. Thus, exclusive of directly sex-linked traits, there is a strong indication of some overall genetic factor, arising at the cellular level, which causes virtually every major disease to act differently in the two sexes, irrespective of environmental influences, and with the inherent advantages usually and largely in favor of females. But what is this overall "sex factor" which is set in motion by the initial XX and XY chromosome differentials? Is it produced in different strengths or degrees, so that one could grade individual males and females accordingly, and estimate their relative chances of susceptibility or resistance to specific ailments and mortality threats? And does this pervasive biochemical sex factor in any way contribute to sex differences in normal mental functioning, behavior or achievements? Surely these are provocative questions. But again I might note that research on these points has been impeded by an especially strong bias. That is to say, as a concomitant both of environmentalism in general, and of the upsurge of *feminism* at the same time, it has been distinctly unpopular in the social sciences to suggest, or undertake research to prove, that psychological and behavior differences between the sexes might be due to anything but training and social conditioning. Indeed, the old familiar slogan, "*Vive la différence!*" has been changed in modern intellectual circles to "*A bas la différence!*"

In a great many other ways human genetics is a wide open field, with many challenging areas to be explored, and many opportunities to make its *future* future exciting and rewarding. What we can also say, on the optimistic side, is that much of the prejudice or indifference which has so far hampered our science is diminishing. Here are some of the reasons:

(1) Medical men are becoming increasingly aware that inherited differences among individuals play an important part in degrees of susceptibility or resistance to almost every condition, and that knowledge regarding these individual factors may help enormously in establishing causes of diseases, and finding treatments or cures.

(2) Psychologists are realizing that the prevailing tendency to seek only environmental causes for emotional and nervous disorders, reading and speech difficulties, delinquency, sexual aberrations, alcoholism, etc., may hinder the discovery of any possible organic factors which may be involved.

(3) As environments continue to become more equalized for human beings, and acquired differences are reduced, genetic differences are certain

to manifest themselves more, to assume more importance and to demand greater attention.

(4) Opposition from religious and other sources has been lessening with the growing tendency among geneticists to take a conservative and restrained attitude toward selective breeding and eugenic measures, and to view population control more as a social than a genetic problem.

(5) The present great concern over the genetic effects of atomic radiation has markedly stimulated interest in human genetics.

Finally, whatever the future of our science may be, if it is to strengthen its position now, it must turn from any lingering tendencies to view human beings mainly as *biological* specimens. People are far more than that. Their heredity cannot be studied, nor can the genetic facts concerning them be applied, without a full understanding of their thoughts, feelings, desires, hopes and social relationships. In sum, to render its greatest service, to enlist the maximum support for itself, and to realize its fullest possibilities, human genetics as a science must strive to make itself as *human* as possible.

Addenda et corrigenda

In Part II of the Proceedings, the paper by *L. L. Cavalli-Sforza* should be followed by a Discussion which should have appeared on page 243:

Discussion

C. Gini (Rome) calls the attention to the fact that emigration is selective in character. In many countries emigrants are mainly recruited from the larger families and, as fertility is, to a certain extent, determined by heredity, it is to be expected that the marriages of the immigrants are more fertile than those of the resident population. Moreover, some data from human populations, supported by observations from other animal species, suggest that the impulse to emigrate is positively correlated with the impulse to marry and with fertility. Often the emigrants are superior to the resident population with regard to normal physical and psychical characteristics, while it is obvious that feeble and ill persons are less inclined to emigrate than those who are strong and in good health. All these circumstances must not be lost sight of when comparing the fertility of the native population with that of marriages in which one of the partners is an immigrant, or the fertility of consanguineous marriages with that of the general population in which the immigrants are included. It is possible and in some cases certain that the differences are due, at least in part, to heterosis, but the selective character of emigration may also have some influence.

In the paper by *H. Lehmann* (Part II, pp. 257-273), the following misprints should be corrected:

Page 261: Fig. 3: transpose the letters *J* and *K* in the line "Haemoglobin: ..."

Page 271: line 2: read "*haemoglobin C*" instead of "*haemoglobin S*".

Page 272: last paragraphe but one: it has been stated here that *haemoglobin J* was found in Algerian Muslims; this is now known to have been *haemoglobin I*.

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A SECOND INVESTIGATION INTO THE CHILDREN OF COUSINS

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An earlier investigation concerning patients admitted to mental hospitals who were found to be children of cousins has already been reported (*Shields and Slater* [1956]). The present communication reports the results of a continuation of this work. For a discussion of the theoretical background and the general methods of the investigation the earlier report should be consulted; but the following explanation may be given at this place.

When the National Health Service was introduced in Britain, in July 1948, mental hospitals were required to complete an enquiry card in respect of every patient admitted. Among the questions asked was one enquiring whether the parents of the patient were related by blood. The information so obtained was transmitted to the General Register Office; and from this Office, by the kind permission of the Registrar-General, a list of hospital registration numbers of patients stated to be of consanguineous parentage was made available to the Genetics Unit. This list included patients admitted to all mental hospitals in the four Metropolitan Regions, *i.e.*, in an area covering Greater London and south-east England.

It was then the task of the Unit to get in touch with the hospitals and obtain from them the names of the patients to whom the registration numbers referred, and the names and addresses of their nearest relatives. The collection of material extended over the five complete years January 1949 to December 1953 inclusive. Unfortunately, it cannot be claimed that we ascertained more than a part of the total consanguineous material

entering these hospitals during this time. The data coming from some hospitals were so scanty and unreliable, or so hedged about with insurmountable difficulties of procedure, that they could not be utilised at all. The data from 12 hospitals were utilised up to 31 August 1951 for the report of *Shields and Slater (loc. cit.)*; the present communication is based on material from 27 hospitals (including 7 of those involved in the first series) beginning from 1 September 1951 up to 31 December 1953. Patients who had been ascertained and reported in the earlier (*Shields and Slater*) series and who were independently re-ascertained in the present series have been excluded from the latter, so that the two series are supplementary to one another. All but two of the hospitals involved are ordinary statutory mental hospitals; the two remaining stand apart in that they exercise some degree of selection on the type of patient they admit. They are the Bethlem Royal and Maudsley Joint Hospital (where the Genetics Unit is located), which contributed 44 proband cases to the earlier series and 38 to the present one; and Holloway Sanatorium, which contributed 18 proband cases to the present series only.

There are certain differences between the first series and the second. All the 12 hospitals whose material was used in the earlier series have their catchment areas in Greater London: they were, however, exceptionally productive, so that the seven which contributed to the present series account for 43% of the cases included in it. Nevertheless, the population covered by the earlier investigation was more exclusively urban than that of the present report. Furthermore Bethlem-Maudsley material made up a relatively larger part of the first series, and would include a relatively high proportion of cases of early psychosis and of neurotic and psychopathic illnesses (this tendency being offset to some extent, however, by the contribution of Holloway Sanatorium to the second series). In fact, schizophrenia, affective psychoses, and organic and symptomatic psychoses made up 64% of the first series (propositi and controls), and 77% of the second series; neurosis and psychopathy accounted for 28% and 19% respectively.

The investigations carried out on the patients themselves in the present series were less complete than those reported earlier. Apart from ascertainment of nature and degree of parental consanguinity (in nearly all cases by correspondence) for the propositi of the present series, no further information was obtained from patients or their relatives, and no family visits were paid. On the other hand, every effort was made to collect all the medical, psychiatric and familial and social information about the patients which could be obtained from any available hospital and other records.

This meant tracing the records of earlier and subsequent admissions of these patients, obtaining the hospital records of relatives known to have been admitted to mental hospitals, etc. (in some cases with the cooperation of hospitals not otherwise involved in the investigation; we here make grateful acknowledgement for their assistance to the Medical Superintendents and staffs concerned). Valuable information was in some cases given by psychiatric social workers, probation officers and others, to whom also our thanks are due. The information for each case was summarised, and has been used for re-diagnosis and statistical analysis.

As explained in the earlier report, a group of control cases, equal in number to the group of *propositi* of ascertained and verified parental consanguinity, was obtained by selecting for each such *propositus* the patient with the next following hospital registration number (it being verified that the answer to the enquiry card question about parental consanguinity was not in the affirmative for such patients); the control patients were then investigated in exactly the same way as the *propositi*. The same procedure was followed for the present series; in what follows, therefore, and in the Tables, it is convenient to designate the various groups of patients according to the following scheme:

- P: *propositi*, of consanguineous parentage
- C: controls
- S: the earlier series (*Shields and Slater*)
- N: the present series (*Nixon and Slater*)
- 1: first-cousin consanguinity or closer
- 2: consanguinity more remote than first-cousinship
- T: total, all types of consanguinity

Thus P_2N symbolises the group of patients in the *present* series (N) who are *propositi* (P) of parental consanguinity *more remote than first-cousinship* (2); and C_TS the *whole* group (T) of *control* patients (C) in the *earlier* series (S).

Type of Consanguinity

In the present investigation, a total of 242 patients was ascertained to be of consanguineous parentage, the degree of consanguinity being that of first-cousins or closer in 167 cases (P_1N), and of remoter degree in 75 cases (P_2N). The distribution is shown in Table 1. It is interesting to take special note of the patients in group P_1N who arose from matings between persons

more closely related than first-cousins, of whom there were 7. The patient who descended from double-first-cousins was a catatonic schizophrenic; in the grandparental generation two brothers had married two sisters. The three marriages between uncle and half-niece and the marriage between uncle and niece all occurred in Jewish families; in one of the uncle/half-niece marriages, the half-niece was also her husband's first-cousin once removed, the patient herself suffering from endogenous depression. In the other two uncle/half-niece marriages, the patients were a male hebephrenic

Table 1. Type of Parental Consanguinity (*N Series*)

Group	Consanguinity	No. of cases
P ₁ N (167 patients)	First-cousins (type known)	125
	First-cousins (type unknown)	35
	Double-first-cousins	1
	Uncle/half-niece	3
	Uncle/niece	1
	Father/daughter	2
P ₂ N (75 patients)	Half-first-cousins	3
	First-cousins once removed	4
	Second-cousins	32
	Second-cousins once removed	2
	"Cousins", etc.	34

and a female epileptic respectively. The offspring of the uncle/niece marriage was a male paranoid schizophrenic. There were two patients who came from incestuous relationships between father and daughter. In one of these the father was a psychopath and had served a prison sentence for incest with several of his daughters, as well as one for violent crime; his son-grandson, our propositus, was one of three full brothers by this union, all of them being severe psychopaths. In the other case of father/daughter incest, there had been no discovery by the police, but the facts were known to other members of the family, and were revealed in the course of an interview sought by the relatives themselves to explain the facts; the child of the union, our propositus, was seen as an out-patient at the age of 28 at a psychiatric clinic, where he had been referred by the Ministry of Labour because of employment difficulties; he was found to be feeble-

minded and suffering from a moderately advanced congenital cerebellar degeneration. It is perhaps noteworthy that in 3 of these 7 cases the patient suffered from schizophrenia.

As in the previously-reported series, there was in the present series an excess of first-cousin marriages of known type in which the couple were the children of two sisters. Putting the sex of the paternal grandparent first, the distribution of type of first-cousinship among the parents of our *propositi* was: *mm* 33, *mf* 20, *fm* 33, *ff* 39. The excess of *ff*-type first-cousinship is, however, much less marked in the present series. The great excess reported in the earlier communication was there tentatively explained by a prejudice both against the marriage of cousins and against marriage between persons of the same surname, a prejudice which would operate selectively in favour of the *ff*-type of relationship in which the common grand-parental surname is most hidden. In the present series on the other hand, ascertainment of the exact relationship could not be pursued so closely as in the earlier series where relatives were interviewed personally, and the fact that the common surname is hidden in the *ff*-type may have led to ignorance among relatives of more than the bare fact of first-cousinship. This explanation is borne out by the larger proportion of first-cousinships of unknown type (22%) in the present series in comparison with the earlier series (16%). In any case, the distribution over the four types given above is not outside the limits set by the results published by other investigators and mentioned in the earlier report.

Type of consanguinity was checked against sex of *propositus* and against diagnosis to see whether there was any indication of the manifestation of sex-linked genes. No such indication was found.

Table 2. Religious Affiliation of Patient (*N Series*)

Group	P ₁ N	C ₁ N	P ₂ N	C ₂ N	P _T N	C _T N
Church of England	113	124	58	56	171	180
Roman Catholic	11	20	4	8	15	28
Nonconformist	19	11	7	6	26	17
Jewish	14	6	4	4	18	10
Other	5	3	1	0	6	3
Not known	5	3	1	1	6	4
Totals	167	167	75	75	242	242

Religious Affiliation

The figures relating to religious affiliation are given in Table 2. It will be noted that, as in the previously-reported material, there is an excess of Jews, Nonconformists and members of religious minorities, and a deficiency of Roman Catholics among the consanguineous patients.

Diagnosis

The distribution of diagnoses is given in Table 3. The proband cases listed together under "Miscellaneous" are of some genetical interest. They include the case of cerebellar degeneration issuing from an incestuous

Table 3. Diagnosis (*N Series*)

Diagnosis	P ₁ N	C ₁ N	P ₂ N	C ₂ N	P _T N	C _T N
Schizophrenia	43	26	23	19	66	45
Endogenous depression and manic-depressive psychoses	35	47	17	14	52	61
Involuntional depression	9	17	6	6	15	23
Reactive depression	10	3	3	4	13	7
Organic and symptomatic psychoses	33	42	18	17	51	59
Epilepsy	3	3	1	1	4	4
Mental deficiency	4	2	1	1	5	3
Psychopathic personality	11	9	3	7	14	16
Neuroses	14	18	3	6	17	24
Miscellaneous	5	—	—	—	5	—
Totals	167	167	75	75	242	242

union already mentioned, one case of narcolepsy, one case of cerebral diplegia, one case of Wilson's disease, and one case of (?) amyotrophic lateral sclerosis. The subject of Wilson's disease is a case of considerable clinical interest. He suffered from a schizophrenia-like psychosis with ideas of reference and influence, and had auditory hallucinations; it is probable that the case will be reported in another place. The case of amyotrophic lateral sclerosis was that of a woman admitted to a mental

hospital at the age of 60 on account of altered behaviour and memory defect for the past two years. On examination marked wasting of the muscles of the shoulder girdle on both sides was found, together with general weakness of the right leg, especially in flexion of the hip and dorsiflexion of the foot, increased knee-jerks, ankle-jerk present on the right but not obtained on the left, plantar response extensor on the right and flexor on the left. Mentally she was mildly euphoric, disoriented, given to confabulation, and unable to care for herself adequately. Over 9 months of observation there was little change: the paralysis progressed slowly and her mental state did not improve.

With regard to the other diagnostic groups, it will be observed that there is no systematic shift from controls to propoiti apart from that observed in *schizophrenia*. The difference between P and C groups is in this respect significant. As this material is supplementary to that provided by *Shields and Slater*, it is in order to take the two series together. This is done in Table 4.

Table 4. Frequency of Schizophrenia (*N and S Series*)

Group	Diagnosis		Proportion Schizophrenia	u	P
	Schizophrenia	Other.			
P ₁ N	43	124	0.257 ¹		
C ₁ N	26	141	0.156		
P ₂ N	23	52	0.307 ¹		
C ₂ N	19	56	0.253		
P _T N	66	176	0.273	2.10	0.018
C _T N	45	197	0.186		
P ₁ S	16	76	0.174		
C ₁ S	16	76	0.174		
P ₂ S	8	13	0.381 ¹		
C ₂ S	2	19	0.095		
P _T S	24	89	0.212	1.03	0.152
C _T S	18	95	0.159		
P ₁	59	200	0.228		
C ₁	42	217	0.162		
P ₂	31	65	0.323		
C ₂	21	75	0.219		
P _T	90	265	0.254	2.50	0.006
C _T	63	292	0.177		

¹ These figures exceed 0.24, which is the upper 2% limit of 0.177.

In three out of the four consanguineous groups, namely P_1N , P_2N and P_2S , the frequency of schizophrenia exceeds the 2% upper limit (one-tail) of the frequency observed in the combined total of all the control groups. The significance of differences in proportions of schizophrenics between P and C groups may be tested by an approximate test using the arcsine transformation and giving values u of the normal deviate to which a probability level P may be assigned. This test shows a highly significant difference between the total proportions in the N series, and no significant difference between those of the S series; but when both series are combined, as can and should be done, the level of significance is increased to the point where the probability of explanation as a chance effect is reduced to 0.7%.

It occurred to the authors that an unwitting and unintended bias might have been introduced into the diagnosis of schizophrenia. As has been stated, all the cases in both investigations were rediagnosed (by E. S.) on the basis of all available documentary material. In order to check whether there had been any such bias, all cases were reclassified on the basis of the hospital diagnosis, the last in point of date being taken if there was more than one diagnosis in any case. It was found that, in fact, the diagnosis of schizophrenia was more favoured by us than by the hospital diagnosticians; but this was so consistently in all groups, both P and C, to an equal extent. The proportions of schizophrenics diagnosed by hospital psychiatrists were, in the several groups:

P_1N 0.246	P_2N 0.253	P_TN 0.248	P_1S 0.163	P_2S 0.429	P_TS 0.212	P_T 0.237
C_1N 0.126	C_2N 0.240	C_TN 0.161	C_1S 0.152	C_2S 0.143	C_TS 0.150	C_T 0.158

These figures and the differences involved are no less significant than those given in Table 4. Our changes in diagnosis, needless to say, went in both directions, in diagnosing patients as not schizophrenic who had been diagnosed as schizophrenic by their hospital psychiatrists, as well as the other way round, though not quite so frequently. However, in the great majority of cases our diagnosis and the hospital diagnosis were the same, the agreement, measured as a correlation coefficient, being in the various groups, both *propositi* and controls, in either series, between 0.70 and 0.84. For those who are interested in this demonstration of impartiality Table 5 is provided.

These findings make it appear to us highly probable that schizophrenia is, in fact, more common in the children of consanguineous parents than it is in the general population. There has not been much work on this subject. *Kallmann* [1938] found no increase in consanguinity in the parentage of 1047 Berlin schizophrenics, but has reported [1946] that of 211 twin

Table 5. Changes of Diagnosis for Schizophrenia (*N* and *S* Series)

Schizophrenia		Diagnosed by E. S.			
		Propositi		Controls	
		Yes	No	Yes	No
Diagnosed by Hospital	Yes	74	10	47	9
	No	16	255	16	283
		$r = 0.80$		$r = 0.75$	

index pairs without schizophrenia in their known ancestry, twelve sets (5.7%) originated from consanguineous matings. Munro [1938] has said that he found schizophrenia more frequently in the children of cousins than in a control series, but did not give precise figures. Strömberg [1938] found that of 123 schizophrenics, in whose cases it had been established with certainty whether or not the parents were related, there was such a relationship in 8 cases—6.5%, as compared with 1.3% for the general population. One is accordingly led to suppose that there is a connection between consanguinity of parents and an enhanced risk of schizophrenia for the children, and a genetical explanation of the connection lies closest to hand.

The next step was to see whether there were any clinical differences between the schizophrenics of the P groups and those of the C groups. If recessive genes are responsible for some forms of schizophrenia, and not for other, one might expect to find the excess of schizophrenics in the P groups to be concentrated in some particular class which could be defined in clinical terms. Thus, on the basis of our present knowledge of the genetics of schizophrenia, one might think that in the P groups the excess of schizophrenics would be found predominantly among the hebephrenics or catatonics, among patients falling ill at an early age, or among those who deteriorated consistently.

In fact, however, no such differences were found. Table 6 gives the distributions when the cases are classified by *Kraepelinian type*. There is no excess of hebephrenics in the P groups compared with the C groups; and while there are excess numbers of P catatonics and P paranoid schizophrenics, the differences are readily accounted for by chance.

The distribution of *ages at first admission* to a psychiatric hospital or clinic, arranged in decades, is given in Table 7. The differences between the

Table 6. Frequency of Schizophrenia, Kraepelinian Types (*N and S Series*)

Group	P ₁ N	C ₁ N	P ₂ N	C ₂ N	P _T N	C _T N	P _T S	C _T S	P _T	C _T
Hebephrenic	18	12	4	8	22	20	8	7	30	27
Catatonic	8	5	7	5	15	10	8	3	23	13
Paranoid	17	9	12	6	29	15	8	8	37	23
Totals	43	26	23	19	66	45	24	18	90	63

P and the C groups are of a random kind; 65% of the P and 64% of the C patients had ages of first admission under 30.

It was impossible to classify *outcome* more precisely than by dividing the schizophrenic patients into the two classes of those who when last heard of had left hospital, and those who were still in hospital or had died. In the P_TN groups these numbered 35 and 31 respectively, in the C_TN group 28 and 17; adding in the S material we get totals of 49 and 41 as against 37 and 26. The C groups have a somewhat better outcome than the P groups, but not significantly so.

Table 7. Schizophrenics: Age of First Admission to Psychiatric Hospital

Age (years):	10-19	20-29	30-39	40-49	50 +	Total
P _T N	8	35	12	8	3	66
C _T N	9	20	11	3	2	45

The failure to find clinical differences between P and C schizophrenics is far from meaning that such differences did not exist, or that they would not be found in the course of subsequent investigations if looked for in a more sophisticated way than was possible for us. Our material was not suitable for the determination of Kraepelinian type, and it is quite probable that this classification does not correspond in any more than a very loose way with genotypic differences. Our estimate of outcome is excessively crude; and with regard to age of onset, the age of first admission to a

psychiatric hospital is clearly a good estimate only in those cases in which the illness begins abruptly and severely from a state of health.

Sex Distribution

In 11 of the total of 32 hospitals from which the total material of both series was drawn, there were separate admission registers for male and for female patients; in these hospitals, therefore, as a consequence of our method of selecting control cases, the sex of the propositus determined the

Table 8. Sex Distribution by Diagnosis (N and S Series)

Diagnosis	P _T N		C _T N		P _T S		C _T S		P _T		C _T	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Schizophrenia	33	33	16	29	11	13	6	12	44	46	22	41
Endogenous affective psychoses, incl. manic-depression and involutional melancholia	18	49	29	55	6	24	10	26	24	73	39	81
Organic states, incl. symptomatic psychoses, cerebrovascular disease, senile and presenile dementia, mental deficiency, epilepsy, etc.	32	33	18	48	10	18	8	18	42	51	26	66
Neuroses and psychopathic personality	18	26	23	24	20	11	22	11	38	37	45	35
Totals	101	141	86	156	47	66	46	67	148	207	132	223

sex of the corresponding control. In terms of cases, this was so in 88 cases out of 242 in the N series, and in 56 out of 113 in the earlier S series. It is, however, permissible to compare the sex distributions in propiti and controls classified by diagnosis, as it was seldom that the diagnosis was the same in the two members of a propositus-control pair. The breakdown of the

figures for sex distribution by diagnosis is given in Table 8, both for the N and for the S series. It will be noted that the sex distribution is more equal for the propoiti than for the controls, and that among the latter there is a larger preponderance of females.

If we eliminate all material in which the propoitus-control pairs were obligatorily of the same sex, we are reduced in the N series to 75 male and 79 female propoiti, and 60 male and 94 female control cases; in the S series, the corresponding figures are 25 male and 32 female propoiti, and 23 male and 34 female control cases. The difference in sex-ratio in the N series between propoiti and controls is relatively large, but does not reach statistical significance. In the N and S series together the proportion of males among the propoiti is 0.47, and among the controls is 0.39.

Table 9 shows the proportions of males, for the whole material from both series of cases, within the broad diagnostic groupings of schizophrenia, affective psychoses, organic states, and psychopathic and neurotic states. Within these diagnostic groupings, subgroups tend to show similar deviations from sex equality: thus the very large preponderance of females shown in Table 10 for the affective psychotics was of about the same degree for manic-depressives, involutional depressives, and depressives of other types.

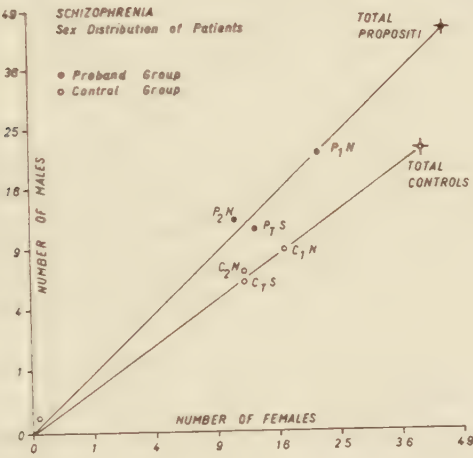
Table 9. Proportion of Males by Diagnosis (*N and S Series*)

Diagnosis	P _T N	C _T N	P _T S	C _T S	P _T	C _T
Schizophrenia	0.50	0.36	0.46	0.33	0.49	0.35
Endogenous affective psychoaes	0.24	0.35	0.25	0.28	0.25	0.33
Organic states	0.49	0.24	0.36	0.31	0.45	0.28
Neurosis and psychopathy	0.41	0.49	0.65	0.67	0.51	0.56

Between the broad diagnostic groupings, on the other hand, there appear to be definite differences in respect of comparative sex ratios as between propoiti and controls: a χ^2 test shows that the heterogeneity is significant at the 5% level. Thus the schizophrenic and organic propoiti show very different sex ratios from those of controls with the same diagnosis, whereas the sex ratios for the affective and the neurotic and psychopathic propoiti are much the same as those of the similarly affected

Table 10: Sex Distribution of Schizophrenics (*N* and *S* Series)

	P ₁ N	C ₁ N	P ₂ N	C ₂ N	P _T N	C _T N	P ₁ S	C ₁ S	P ₂ S	C ₂ S	P _T S	C _T S	P _T	C _T
NO	21	9	12	7	33	16	7	5	4	1	11	6	44	22
OA	22	17	11	12	33	29	9	11	4	1	13	12	46	41
Totals	43	26	23	19	66	45	16	16	8	2	24	18	90	63



controls. Since in the case of conditions determined by autosomal recessive genes one might well expect the sexes to be equally represented, the suggestion arises that genetic factors of this kind are most likely to be found among patients suffering from schizophrenia and from organic states. The sex ratios for schizophrenia are particularly interesting, and Table 10 and Fig.1 show that their values, and the difference between P and C values, are consistent for the independent groups N_1 , N_2 and S_T . If the difference between P and C sex ratios for the schizophrenics in the whole material (*N* and *S* series combined) is tested for significance by means of the arcsine transformation we get a normal deviate value of 1.7, with associated (one-tail) probability 0.04.

Marriage and Fertility

It was found that fewer of the *propositi* than of the controls married, and if they did marry they tended to have fewer children; the relevant data are given in Table 11, in which the data from the N series and the S series have been summed. There are small differences between the distributions of marital status by age of the P and of the C cases, but these

Table 11. Marital Status and Fertility of *Propositi* and Controls (*N* and *S* Series, totals)

Age Group	Single		Married		Married, no. of children known		Total of children		Mean no. of children	
	P	C	P	C	P	C	P	C	P	C
Under 20	17	24	—	—	—	—	—	—	—	—
20-24	20	11	—	4	—	4	—	3	—	0.75
25-29	19	13	9	10	9	10	12	14	1.33	1.40
30-34	11	6	11	17	11	17	15	29	1.36	1.71
35-39	15	5	22	21	20	21	28	36	1.40	1.71
40-44	11	4	18	21	16	20	19	43	1.19	2.15
45-49	14	4	10	18	9	15	13	26	1.44	1.73
50-54	8	3	17	15	14	14	26	25	1.86	1.79
55-59	5	5	9	15	8	11	13	31	1.63	2.82
Over 60	10	11	33	52	26	33	63	95	2.42	2.88
Totals	130	86	129	173	113	145	189	302		

are very far from enough to account for the wide divergence found. Thus if the age distribution of the P cases is equated with that of the C cases, the observed number of 129 persons married becomes the corrected number of 132.5. The comparison, 133/259 in *propositi* against 173/259 in controls, yields a χ^2 of 12.80 for 1 degree of freedom, and is highly significant.

If the married *propositi* had had fertilities, equal at corresponding ages, with those of the control patients, they would have had 238.0 children instead of the observed 189; in other words their fertility was 79.4 % of that of the controls, a deviation which yields a χ^2 of 10.08 for 1 d.f. The reduction in fertility was general, and was not exhibited, as perhaps might have been expected, in an excessive proportion of childless marriages.

The schizophrenic propoiti shared in the general tendency towards celibacy, compared with the schizophrenics of the C groups; but the difference between proportions of persons married was only significant in the N_1 series at the .05 level of probability, just falling short of this in the combined N and S totals.

Discussion

On the hypothesis that autosomal recessive genes play a part in the aetiology of schizophrenia, it could be expected that there would be an excess of schizophrenia in persons admitted to mental hospitals, who were the children of consanguineous matings, compared with a group of randomly chosen admissions. Such an excess of schizophrenia has in fact been found, with a probability of less than 1 per cent that it could be accounted for by chance. The hypothesis therefore receives a measure of confirmation.

The schizophrenic propoiti deviate also from the schizophrenic control patients in showing an approximately equal number of males and females, instead of a large female preponderance. This difference between the two groups is constant in all sub-groups, and in the total material is significant at the 0.04 level. Equality in the representation of the sexes in the consanguineous material accords well with hypotheses involving autosomal recessive genes.

One might have expected that there would be clinical differences between the schizophrenics of the P and the C series, if recessive genes played a larger part in aetiology in the one series than in the other. No such clinical differences have been found. It is more likely that this negative finding is due to inadequacies of clinical investigation and record, than that such differences would not be found, if looked for more carefully and skilfully than was possible with this material.

While the findings reported here would be most simply explained if autosomal recessive genes played a part in the aetiology of schizophrenia, there are other possible explanations. If those who married cousins were more frequently mentally abnormal than others, and if they passed on to their children, through the germ cell or through early environment, a predisposition to schizophrenia, the observed differences between propoiti and controls could perhaps be accounted for. However, the parents of our propoiti were not significantly more frequently mentally abnormal than the parents of patients in the control series; and there was no relative excess of schizophrenia in the children of parents one or both of whom were abnormal. This hypothesis is, therefore, not very plausible.

If we explain the excess of schizophrenia in the propoiti as caused by the segregation of one or more autosomal recessive genes, then we can make some estimate of the gene frequency. For this purpose only the data on those patients who were children of first cousins, and their controls, are used. We may write:—

- s_c = the proportion of general admissions diagnosed schizophrenic;
- s_p = the proportion of propoiti (children of first-cousin marriages, S and N series combined) diagnosed schizophrenic;
- x = the frequency of first-cousin marriage in the parents of schizophrenics in the general population;
- m_c = the proportion of general admissions diagnosed non-schizophrenic;
- m_p = the proportion of propoiti diagnosed non-schizophrenic;
- a = the frequency of first-cousin marriages in the parents of non-schizophrenics.

Schizophrenics and non-schizophrenics will then be distributed in the mental hospital intake in the proportion $s_c:m_c$; and by searching for those who are the children of first-cousins we shall ascertain a fraction of the first proportionate to x , and of the second proportionate to a . We may therefore write:—

$$x/a = (s_p \cdot m_c) / (s_c \cdot m_p).$$

Our estimate of a , from the data given by *Shields and Slater*, is 48/8816 = 0.00544; and on the basis of the present material our other estimates are $s_c = 40/251$, $s_p = 57/251$, $m_c = 211/251$, $m_p = 194/251$. From these we obtain the value 0.00844 as our estimate of x . The gene-frequency corresponding with this, calculated by the *Lenz-Dahlberg* formula, is $7.34c$, where c is the frequency of first-cousin marriage in the general population.

The frequency of first-cousin marriage was estimated some years ago by *Julia Bell* [1940] as 0.006 (for general hospital patients in England and Wales). It might well have been smaller than this in a predominantly urban population, and be smaller now than it was then. If we take the value of c as 0.005, then p , the gene frequency, is estimated as 0.0367; if we prefer 0.004, then p becomes 0.0294. With the higher value of p , the frequency of the homozygote is calculable as 0.0013. The frequency of schizophrenia itself has been estimated in a number of comparable countries, but most reliably in Germany as 0.008. The frequency in Britain is not likely to be widely different. This would lead to the conclusion that, even with a 100% rate of penetrance, only about one-sixth of the totality of schizophrenia

could be accounted for on the autosomal recessive hypothesis. If the rate of cousin marriage in Britain is lower than 0.005, or if not one but a number of autosomal recessive genes are involved, then the proportion of the totality of schizophrenia to be laid to the charge of autosomal recessive genes would be smaller.

No great reliability is claimed for these values, which are based on small numbers of persons investigated. Nevertheless one may say that estimates of gene frequency may be made by this approach, which has provided evidential support for certain conclusion which are of some importance to medicine. These are that the group of conditions which we call schizophrenia is probably genetically heterogeneous, that it probably includes a proportion of cases attributable to autosomal recessive genes, but that this proportion is not very great. Work which would be of value in confirming or rebutting these conclusions would be further investigations of the frequency of cousin marriage in the parents of schizophrenics, and of the frequency of schizophrenics in the children of cousin marriages.

Summary and Conclusions

An investigation is described into patients admitted to psychiatric hospitals who were ascertained to be the children of cousins. It represents a continuation of earlier work by *Shields and Slater* [1956]. Propositi so obtained were matched with control cases.

In the first-cousin marriages, the type of consanguinity most commonly found was, as in work by other observers, the marriage of the children of two sisters. There were also children of marriages between uncle and half-niece, uncle and niece, and of incestuous unions between father and daughter.

Type of consanguinity brought into relation with sex and diagnosis of propositus showed no indication of the operation of sex-linked genes.

Jews and other religious minority groups were over-represented and Roman Catholics were under-represented among the propositi.

Comparison of diagnoses in propositi and controls showed an excess of schizophrenia in the former, statistically significant both in the present series and in the summed results of the present and the earlier series. Taking the summed series, in the propositi there were 90 schizophrenics in a total of 355 cases, in the controls 63 schizophrenics in a total of 355.

The significant difference (at the 0.01 level) remains when hospital diagnoses rather than our own diagnoses are considered.

These findings would appear to support the hypothesis that autosomal recessive genes play some part in the aetiology of schizophrenia.

No clinical differences were found between the schizophrenics who were *propositi* and those in the control group.

The schizophrenic *propositi* were equally distributed between the sexes; the control schizophrenics showed a marked preponderance of females. This difference is significant at the 0.04 level. The finding is consistent with the recessive hypothesis.

Propositi were more frequently single, and if married tended to have fewer children, than control patients.

The data obtained enable one to estimate that the frequency of first-cousin marriage in the parents of schizophrenics is of the order of 0.008; on the single-gene hypothesis this would lead to an estimate of the gene frequency of about 0.03. If the frequency of schizophrenia in the general population is about 0.008, one-sixth of the totality of schizophrenia could be accounted for by the recessive gene. It is emphasised that these estimates are very provisional.

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Zusammenfassung

Vorstehende Arbeit ist ein Bericht über Patienten psychiatrischer Hospitale, die einer Ehe zwischen Vetter und Base entstammen, und stellt eine Fortsetzung früherer Studien von *Shields* und *Slater* (1956) dar. Derartige Patienten sind mit Kontrollfällen verglichen worden.

Die häufigste Form der Blutsverwandtschaft in Vetter-Base-Ehen war, wie auch von anderen Untersuchern festgestellt, eine Heirat zwischen den Kindern zweier Schwestern. Es fanden sich jedoch ebenfalls Kinder aus Ehen zwischen Onkel und Halbnichte, Onkel und Nichte und aus blutschänderischen Beziehungen zwischen Vater und Tochter.

Ein Vergleich zwischen Art der Blutsverwandtschaft einerseits und Geschlecht und klinischer Diagnose des Kranken andererseits wies nicht auf die Wirkung eines geschlechtsgebundenen Gens hin.

Unter den Probanden waren Juden und andere religiöse Minoritäten im Übermaß, Katholiken in der Minderheit vertreten.

Ein Vergleich beider Gruppen – Blutsverwandte und Kontrolle – zeigt ein Übermaß von Schizophrenie in ersterer, das statistisch bedeutend sowohl für die hier berichtete Serie als auch für diese zusammen mit der früheren Serie ist. Insgesamt wurden unter 355 Fällen von Blutsverwandten 90 Schizophrene gefunden, verglichen mit 63 in der Kontrollgruppe.

Der Unterschied bleibt bestehen, wenn statt unserer eigenen Diagnose diejenige des Hospitals berücksichtigt wurde.

Diese Ergebnisse scheinen die Hypothese zu unterstützen, daß rezessive Gene der Autosomen eine Rolle in der Ätiologie der Schizophrenie spielen.

Es wurden keinerlei klinische Unterschiede zwischen den Schizophrenen der Blutsverwandten- und der Kontrollgruppe gefunden.

Beide Geschlechter waren in der Blutsverwandtengruppe zahlenmäßig gleich verteilt, während in der Kontrollgruppe das weibliche Geschlecht merklich überwog. Das Ergebnis steht in Einklang mit der rezessiven Hypothese.

Blutsverwandte Kranke waren öfters unverheiratet, und wenn verheiratet, hatten sie weniger Kinder als Kranke der Kontrollgruppe.

Die obigen Ergebnisse berechtigen zu der Schätzung, daß die Häufigkeit von Vetter-Base-Heiraten unter den Eltern von Schizophrenen etwa 0.008 beträgt: nach der Ein-Gen-Hypothese betrüge die Genhäufigkeit schätzungsweise etwa 0.03. Wenn die Häufigkeit der Schizophrenie unter der Allgemeinbevölkerung etwa 0.008 beträgt, dann würde ein Sechstel aller Schizophrenie durch das rezessive Gen zu erklären sein. Es wird betont, daß diese Schätzungen nur sehr vorläufiger Natur sind.

Résumé

Cette étude au sujet de malades admis dans des maisons d'aliénés et certainement issus de parents consanguins est présentée comme la continuation du travail préalable de *Shields et Slater* (1956). En sus des sujets consanguins on a examiné un groupe témoin de malades non-consanguins.

Les sujets issus des unions entre cousins-germains étaient plus souvent les enfants de deux sœurs, ce que d'autres travailleurs ont déjà trouvé. Il y avait aussi des sujets issus de mariages entre oncle et demi-nièce et entre oncle et nièce, et des unions incestueuses entre père et fille.

La comparaison du type de consanguinité entre cousins-germains avec le sexe et le diagnostic du sujet ne suggère pas l'action de gènes liés au sexe.

Parmi les sujets consanguins les Juifs et les membres des sectes minoritaires se trouvaient en excès par comparaison avec les sujets témoins, mais les catholiques étaient en déficit.

La comparaison des deux groupes, de consanguins et de témoins, révèle un excès de schizophrènes dans le premier groupe; cet excès est significatif. Pour les deux études il y avait 90 schizophrènes parmi 355 sujets consanguins, mais seulement 63 parmi 355 sujets témoins. La différence reste significatif (au niveau de 0,01) selon les diagnostics officiels au lieu de ceux des auteurs.

Ces données peuvent soutenir l'hypothèse que des gènes récessifs prennent part à l'étiologie de la schizophrénie.

Aucune différence clinique n'a été trouvée entre les schizophrènes consanguins et les schizophrènes témoins.

Les schizophrènes consanguins sont également distribués entre les deux sexes, mais chez les schizophrènes témoins il y a avait une prépondérance de femmes; cette différence est significative au niveau de 0.04. Ce résultat est compatible avec l'hypothèse des gènes récessifs.

Les sujets consanguins étaient plus souvent célibataires; mariés, ils tendaient à avoir un plus petit nombre d'enfants par comparaison avec les sujets témoins.

Ces données permettent d'estimer approximativement la fréquence des mariages entre cousins-germains parmi les parents des schizophrènes comme étant de l'ordre de 0,008; d'après l'hypothèse d'un seul gène récessif ce chiffre suggère que la fréquence du gène est autour de 0.03. Si la fréquence de la schizophrénie dans la population générale est 0.008, un sixième de toute la population schizophrénique pourrait être attribué au gène récessif. Ces évaluations ne sont que provisoires.

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A MONGOLIAN MOTHER AND HER CHILD. A CASE REPORT

By R. SCHLAUG

In the discussion of the aetiology of mongoloid idiocy, several investigators have examined the hypotheses concerning hereditary factors through extensive family-researches and numerous studies of twins. No clear-cut results have been obtained, though most of the facts suggest that heredity has nothing to do with the origin of the deformity. For its biological understanding, however, it is most interesting to *study the children of mongoloid parents*. A review of the literature concerned shows that for a mongoloid mother to give birth to a child is an extremely rare event, and there appears to be no description of a mongoloid father. Actually, I have not succeeded in finding more than two certain cases of mongoloid reproduction—*Lelong* [1949], and *Sawyer* [1949]. Vague information as to further examples is to be found in a number of writers (*Rosenberg* [1924], *Weygandt* [1936], *Lind* [1923], *Brousseau* [1928], and others), but the descriptions are not detailed enough to interpret. In the two certain cases, one child was healthy, while the other was a mongoloid idiot like its mother.

In actual fact, mongoloid parents are probably not unique. The deformity is not unusual, and a certain percentage reach the age of sexual maturity. The imbecility is not always so extreme as to necessitate admittance to an institution, and the possibility of conception must therefore exist at some time or other. That mongoloidism does not of itself imply sterility is obvious. The following report is of a mongoloid mother and her child, whom I studied.

A woman of typical mongoloid appearance (see fig. 1) and now 35 years of age, at the age of 29 gave birth to a girl by normal delivery. The pater-

nity was never settled, but strong suspicions* pointed to the woman's father, with whom she lived alone, as being the guilty party.



Fig. 1a

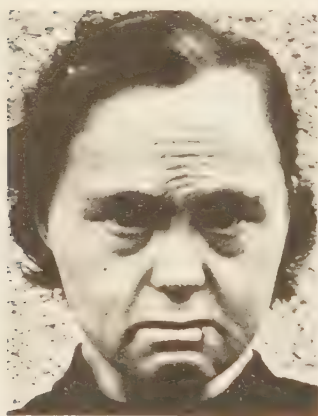


Fig. 1b



Fig. 1c

Fig. 1. The mongolian woman as a child in her family (a), and at the present examination (b).

The woman was born as number 8 in a family of 10 brothers and sisters. The parents were not related, were healthy— as were the woman's brothers and sisters, who, in their turn, had several healthy children.

* Blood groups:	Father	A ₂ B MN S Le (a-).	C+ D+ E- c+
	Woman	B N ss Le (a+).	C+ D+ E- c—
	Child	A ₂ MN S Le (a+).	C+ D+ E- (Doc. R. Grubb, M.D.)
Irides:	Father	brownish	
	Woman	blue	
	Child	brown	

There are no other cases known of mongoloid idiocy or other imbecility or deformity in the family. The mother was 39 years of age at the time of the woman's birth and died some years later of pneumonia. When visited, the father was found to be a simple old man (38 years of age at the time of the woman's birth), but without apparent intelligence defects. Two of his children were visited and were quite normal. The woman's mental deficiency was noticed very early; she developed late, could never go to school and was treated always as a child. She was never admitted to any institution.



Fig. 2

Fig. 2. The right palm of the woman.



Fig. 3

Fig. 3. X-ray picture of the woman's left foot. Only two phalanges on the fifth toe.

On examination, the woman was found to be 140 cm in height and meagre, skull small and rounded and flat at the occiput. Cranium measurements: length 160 mm, breadth 135 mm, biauricular width 120 mm, height 115 mm, distance between pupils 50 mm. Nose was short and thick, with sunken bridge, and the inter-nostril wall protruding, with a lobe down to



Fig. 4a



Fig. 4b

Fig. 4.

The mongolian woman's child at the age of 5.

Fig. 5.

X-ray picture of the child's right leg. Fibula extremely thin.

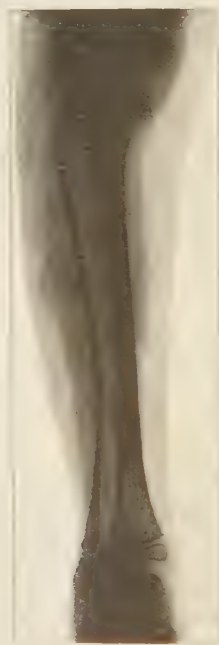


Fig. 5

the upper lip. The mucous membranes of the lips were dry and cracked, mouth rather open, tongue large and thick and protruding. Teeth were small, uneven, with caries and abundant paradentosis. There was no strabism or cataract and no colourblindness (Ishihara). Ears were malformed with fixed lobuli. Skin was dry and coarse, which, together with a bad turgor gave the woman an aged appearance. There was muscular hypotension with hyperflexibility in the wrists. Hands and feet were small and clumsy, the little fingers short with medial-bent outer phalanges. The palm of the right hand was crossed by four-finger-lines (see fig.2). For X-ray picture of left foot see fig.3. Bilateral hallux valgus.

Stethoscopy of the heart and lungs showed normal findings. There were normal reflexes, no paresis.

Mentally the woman presents a picture of pronounced imbecility. She only understands the simplest conversation, her replies are childish and often stereotyped. She has never realized that she gave birth to a child some years ago. She can neither read nor write, but sees to her personal hygiene reasonably well, yet requires supervision like a 5 or 6 year-old child. She likes best to sit in her favourite chair, often smacking her lips, listens to the radio, and recognises simple pieces of music. Under supervision she can help with the simpler household tasks. She is of an even and sunny disposition.

In the course of the years the woman has not had any severe illnesses, but catches cold easily. She has had a tendency towards fatness, but in recent years has lost weight considerably. She had menstrual periods previously, but since her delivery and the accompanying salpingectomy, these have not returned.

The diagnosis of *mongoloid idiocy* with regard to the woman is fairly clear. But the picture presented by her child is more puzzling.

The child, a girl (fig.4), was born by normal delivery, after almost 5 hours labour. Weight at birth 1,920 grammes; 42 cm in height; size of head 29,5 cm. Apart from a small foetal tumour no deformities were observed. The initial loss of weight set in. She had experienced one or two slight asphyctic crises, but otherwise in good general condition and was eating well. When 6 months old, the child was under observation at a children's hospital, where its appearance was considered unusual but not indicating towards mongolian idiocy. She had slight epicanthus, sunken nose-bridge but otherwise no mongoloid stigmata and was in good general condition. She has had no serious illnesses and no epileptic fits.

As it grew older the child did not develop normally. At the present time, at the age of 5, it mostly lies down, can sit up but cannot stand or walk.

Does not talk but can see and hear. She has no control over bladder or bowels, prattles and plays with its fingers, can respond to the nurse's smile: sunny disposition on the whole.

The physical development is very much stunted. She is now 5 years of age but only 89 cm tall, and weighs 10.5 kilogrammes. Circumference of head 46 cm. The physical structure, including the face, has a slight but noticeable lack of symmetry, and the child prefers to lie on its right side. The chest is slightly compressed from the sides, so that the breast-bone protrudes somewhat.

The extremities show no deformities on inspection, but the X-ray reveals strikingly delicate diaphysis, especially the fibulae (see fig.5). The X-ray reveals no sign of rickets in the skeleton. X-ray of the head shows no fontanelles and—for her age—normal closing of the sutures. The dentition is normal. Bone development presents no apparent departures from the normal.* The fold-pattern in the palm of the hands is not abnormal.

The face is slightly asymmetrical, the nose-bridge low, and the upper lips peculiarly shaped. There is nothing distinct, but possibly a suggestion of epicanthus. There is no strabism. The ears are of normal shape, with tied lobes. The hair is abundant and soft.

Physically there are normal findings from the heart, no pareses and normal reflexes and no sensibility impairments.

Thus the child is considerably stunted in her development, both physically und psychically. The general impression does not correspond to the mongoloid type. It has had good care at a children's home, where they have made ambitious attempts to help the child; and where, moreover, she enjoys a certain popularity because of her pretty smile and even temper. She must, however, be characterised as an idiot.

From the description and the illustrations it is clear that, in any case, the child does not present a typical mongoloid picture. In fact, such a diagnosis would scarcely be considered if one knew nothing of the mother's deformity. It is also difficult to obtain criteria for any other specific diagnosis of the child. Severe rickets is as little evident as chronic hypothyreoidism, Rh-lesion or any other well-defined syndrome.

To explain the child's condition, four different groups of possibilities may be considered:

- (1) It is a case of a "partial" syndrome of mongolian idiocy.
- (2) The mother's deformity, already at the germ-cell stage, has produced the setting for an abnormal development on the part of the offspring.

* X-ray pictures were examined by Doc. H. Idbohrn, M.D.

which, however, has not involved a repetition of the mother's deformity but an unspecific abnormality.

(3) The child was normal at conception, but *in utero* or during the earliest stages of growth and independent of the mother's deformity, suffered serious injuries, especially to the brain, which caused disturbances in the child's growth.

(4) A recessive abnormality has been activated through inbreeding.

The first alternative would imply that mongolian idiocy is not such a closely-knit syndrome as is generally supposed. If it were only a question of mongoloidism in the child, one would not expect so complete an idiocy as is here the case. However, it is also possible that the same change in the mother's organs of reproduction which have been held responsible for mongoloidism in general ("the theory of defect nidation") may have been responsible also for this non-mongolic deviation. In the literature on this subject, the only case where a mongoloid mother gave birth to an indisputably mongoloid idiot could be interpreted in a similar way, in which case it would not be necessary to suggest a direct hereditary transmission of mongoloidism.

The second alternative would assume that mongoloid deformity also included the sexual cells—not an improbable assumption. But that is only speculation and could not be easily tested.

The third alternative is in line with previous experience that a mongoloid woman can bear a healthy child. However, there is no anamnestic data or anything definite in the condition which would guarantee a diagnosis of exogenous brain injury. The features which are reminiscent of mongoloidism in the child although vague and difficult to interpret would, of course, if this alternative is the right one, not pertain to this.

The final alternative cannot be supported by any information with regard to abnormality in the family.

Of course, there is no possibility of ruling out with certainty any of the explanations suggested, nor can they be considered mutually exclusive. The foregoing should only be regarded as an attempt to throw some light on this problem which might lead to further discussion.

Summary

A thirty-five year old typical mongoloid woman from a healthy family and her 5-year old child have been examined. The child presents a picture of complete idiocy difficult to interpret but with certain features resembling the mongoloid syndrome.

Zusammenfassung

Untersucht wurden eine 35 Jahre alte Frau aus gesunder Familie mit typischer mongoloider Idiotie und ihr 5 Jahre altes Kind. Das Kind bietet ein Bild vollständiger Idiotie, das schwer einzuordnen ist, aber einige Merkmale aufweist, die denen des mongoloiden Syndroms ähneln.

Résumé

L'auteur a examiné une femme de 35 ans, atteinte de mongoloïdisme typique, issue d'une famille non tarée, ainsi que sa fille de 5 ans. L'enfant présente le tableau clinique d'une idiocie complète, difficile à interpréter, mais avec certains aspects ressemblant au syndrome mongoloïde.

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THE HAGEMAN TRAIT IN A FAMILY WITH HAEMORRHAGIC DIATHESIS

By KNUD-ERIK SJÖLIN

Since *Ratnoff* and *Margolius jr.* [1955] and *Ratnoff* and *Colopy* [1955] published their original papers on three patients with the Hageman trait, four additional cases of this deficiency have apparently been published. *Frick* and *Hagen* [1956] described two males with prolonged clotting time and recalcification time, and with reduced prothrombin consumption. *Ramot, Singer, Heller* and *Zimmerman* [1956] described a male with prolonged clotting time and reduced thromboplastin generation. *Sjölín* [1957] described a male where the thrombin generation test was delayed and became normal after addition of heated absorbed serum. A clotting defect in horse plasma similar to the Hageman trait has also recently been demonstrated (*Sjölín* [1957]). All cases of the Hageman trait published so far have presented no clinical symptoms of a haemorrhagic diathesis. Because of this peculiarity it is of interest to report the investigations of a Danish family with manifest haemorrhagic diathesis classified as haemophilia, where the clotting defect seemed to be caused only by lack of the Hageman factor.

Methods and materials. Quick's prothrombin time was determined according to *Biggs* and *Macfarlane* [1953]. The thrombin generation test was performed as described before (*Sjölín* [1956]): 4½ ml blood was run directly from the cannula into the vein into 0.5 ml sodium citrate solution (3.8%) in a silicone coated glass tube and mixed by gentle inversion of the tube. The citrated blood was centrifuged slightly for two minutes at a maximum speed of 1000 r.p.m. and the plasma separated. Into each of the 13 glass tubes which were of uniform size (internal diameter 8.5 mm, no silicone) 0.4 ml 0.15% fibrinogen solution was poured. The tubes were placed

in a rack in a water bath at a temperature of 37° C. In another test tube 1 ml of the plasma sample and 1 ml saline were mixed, the mixture being allowed to reach the temperature of the water bath. Then 1 ml of preheated (37° C.) calcium chloride solution was rapidly added. The contents of the tube were shaken and a stopwatch started. Beginning at 1 minute after recalcification and then at one minute intervals, 0.1 ml of the reaction mixture was transferred with a micropipette to successive fibrinogen tubes, and the clotting time (t) of the fibrinogen solution in these tubes was recorded. The moment was noted that the reaction mixture clotted. This is the recalcification time of the diluted plasma. The clot was pressed against the wall of the test tube with two wooden sticks during the rest of the procedure. A curve relating the clotting time (t) of the fibrinogen solution to the reaction time (T) of the plasma sample was prepared for each sample. An arbitrary unit of the thrombin was chosen for the purpose of comparing one experiment to another. This unit was given as the reciprocal value of the clotting time (t) of the fibrinogen solution (measured in seconds) and calculated as $600/t$. The concentration of thrombin is roughly proportional to the clotting time of the fibrinogen solution (Astrup and Darling [1942]).

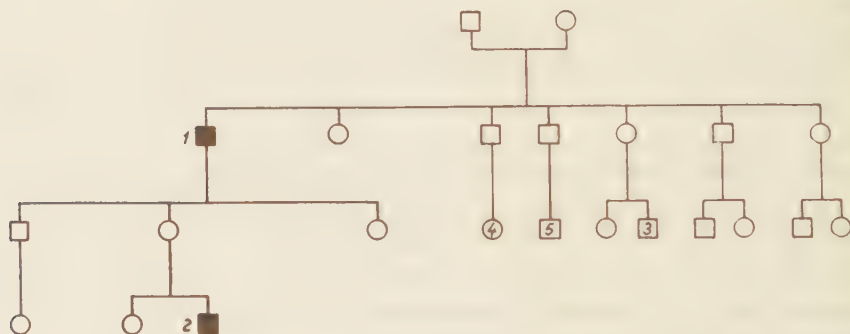


Fig. 1. The pedigree of the family.

Reagents:

Saline: 0.85% NaCl.

Sodium citrate: 3.8% in water.

Calcium chloride solution: 0.025 M $\text{CaCl}_2 \cdot 6 \text{H}_2\text{O}$.

Saline diethylbarbiturate buffer: sodium diethylbarbiturate buffer (Michaelis), 0.05 M, pH 7.8, containing 0.10 M NaCl. Total $\mu = 0.15$.

Absorbed bovine plasma: Prepared with two treatments with 2 g of BaSO_4 per 100 ml according to Brodthagen [1953].

Bovine fibrinogen (Astrup and Müllertz [1952]) was diluted immediately before use to 0.15% fibrinogen with saline diethylbarbiturate buffer. Heated barium sulphate absorbed serum was prepared as described before (Sjölin [1957]). Platelet suspension was prepared according to Sjölin [1957]. Samples of test plasma used in cross matching were centrifuged for 15 min. at 2500 r.p.m. and stored at -20°C .

Test tubes and pipettes were cleaned with sodium carbonate and dichromate-sulfuric acid.

Case reports. Fig. 1 shows the pedigree of the family.

Case No. 1. Male. Born in 1900. The patient has had bleeding accidents from infancy. He had long lasting bleedings from the gums during tooth eruption, melaena, haematuria, intramuscular bleedings, subcutaneous bleedings, long lasting bleedings from small incisions and haemorrhages at the joints, especially the elbows. He has been in hospital several times because of his haemorrhagic diathesis. The patient died at the age of 48, apparently from coronary occlusion.

Case No. 2. Male. Born in 1956. Proband. At the age of 6 months the patient had a bleeding at the left ankle joint. Since then he has had several subcutaneous haematomas. Once there was bleeding from the left knee joint and several times there were haemorrhages at the ankle joints. There were long lasting bleeding episodes during tooth eruption. So far there has been no haematuria, melaena or intramuscular bleedings.

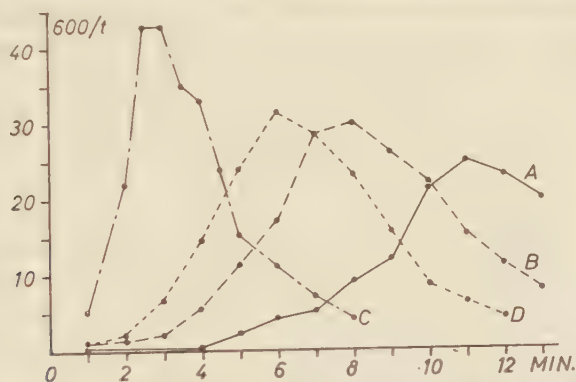


Fig. 2. Thrombin generation test in the patient's plasma. Curve A was obtained with no addition. Curve B was obtained after addition of absorbed bovine plasma. Curve C and D was obtained after addition of normal serum and heated reabsorbed serum respectively.

Abscissa: reaction time in min.

Ordinate: reciprocal clotting time of fibrinogen solutions expressed as $600/t$ (t in sec.).

Laboratory investigations (Case No. 2).

Quick's prothrombin time: 16, 17, 18 sec. (Control: 16 sec.). Thrombocytes: 660,000 per mm^3 plasma. Recalcification time of diluted plasma: 5 min. 53 sec. Fig. 2 curve A shows the results of the thrombin generation

test. The thrombin concentration increased slowly after a lag period of 4 min. The maximum concentration of thrombin, which was obtained after 11 min. was high. Addition of 0.2 ml absorbed bovine plasma improved the thrombin generation considerably. (Fig. 2, curve B). After a lag period of 3 min. the thrombin concentration increased and decreased quickly. The recalcification time was 4 min. The addition of either 0.2 ml normal serum or of 0.2 ml heated reabsorbed serum improved the thrombin generation (Fig. 2, curve C and D respectively). The recalcification times were 1 min. 33 sec. and 1 min. 30 sec. respectively.

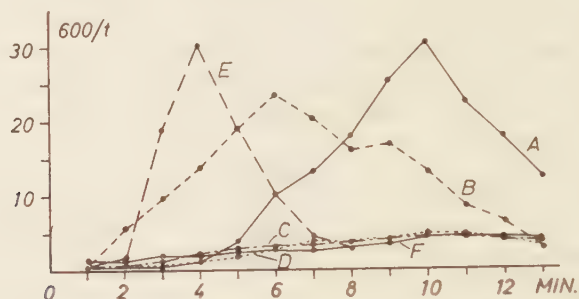


Fig. 3. Thrombin generation in the patient's plasma. Curve A was obtained after the addition of a platelet suspension. Curve B after the plasma had been stored at -20°C . Curve C was obtained after platelet poor plasma had been stored at -20°C . Curve D demonstrates the thrombin generation in platelet poor plasma after the addition of a platelet suspension. Curve E and F show the thrombin generation in plasma with simultaneous AHF and Christmas defect after the addition of our patient's plasma and saline respectively. Values recorded as in Fig. 2.

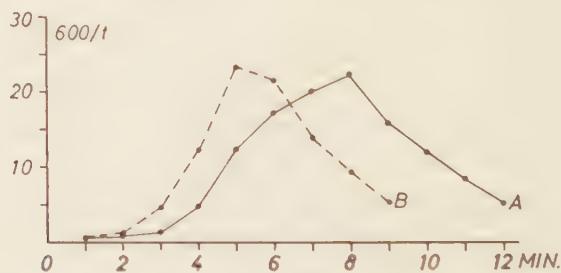


Fig. 4. Thrombin generation in the plasma from the patient's mother (Curve A). Curve B was obtained after the addition of heated reabsorbed serum. Values recorded as in Fig. 2.

Fig. 3, curve A shows the thrombin generation after addition of 0.2 ml frozen platelet suspension ($178,000$ platelets per mm^3 suspension). There

was no significant improvement in the thrombin generation. The recalcification time was 5 min. Fig. 3, curve B demonstrates the thrombin generation of the patient's plasma after it had been stored 48 hours at -20°C . with its normal content of platelets. The thrombin concentration rose and fell in a way which may be called normal. If the test was performed on the patient's stored platelet poor plasma (6,000 platelets per mm^3) there was almost no thrombin formation (Fig. 3, curve C). If 0.2 ml frozen platelet suspension was added to the frozen platelet poor plasma the thrombin generation was not improved (Fig. 3, curve D).

Fig. 3, curve E shows the thrombin generation in a plasma sample from a patient with combined haemophilia (lack of AHF and Christmas factor) (Sjölín [1957]). After the addition of 0.2 ml of the present patient's plasma, the thrombin generation became completely normal, the recalcification time being 2 min. 45 sec. The thrombin generation before the addition of our patient's plasma is demonstrated in curve F.

Fig. 4, curve A shows the thrombin generation in plasma from the patient's mother. The lag period was about 3 min. The thrombin concentration then rose and fell quickly. Recalcification time: 3 min. 50 sec. Curve B shows the thrombin generation after the addition of 0.2 ml reabsorbed heated serum. The generation of thrombin was accelerated. The recalcification time was 3 min. 30 sec.

Discussion

So far 7 cases of the Hageman trait have apparently been published. None of these patients had haemorrhagic diathesis and they have all been found accidentally. In table 1 the most important pathologic laboratory findings are summarized. They all have in common the coagulation time or recalcification time which is prolonged. The thromboplastic activity of the plasma, determined either by the thromboplastin generation test (Ratnoff and Margolius jr. [1956], Ramot and Singer [1956]), the prothrombin consumption (Frick and Hagen [1956], Ramot and Singer [1956]) or the thrombin generation test, (Sjölín [1957]) was delayed.

The prolonged clotting time and the decreased thromboplastic activity were normalized by the addition of heated barium sulphate absorbed serum. As our last patient had symptoms of haemorrhagic diathesis in contradistinction to the other patients with Hageman trait which have so far been mentioned in the literature, the question arises whether the patient has the Hageman trait. The clotting defect in the patient's plasma cannot

Table 1

	Thromboplastin generation test.	Recalcification and clotting time	Prothrombin consumption.	Thrombin generation.
<i>Ratnoff and Margolius jr.</i> 3 cases, 1956	Delayed	Prolonged		
<i>Frick and Hagen</i> 2 cases, 1956		Prolonged	Decreased	
<i>Ramot and Singer</i> 1 case, 1956	Delayed	Prolonged	Decreased	
<i>Sjölin</i> 1 case, 1957		Prolonged		Delayed
<i>Sjölin</i> 1 case, 1957 (present case)		Prolonged		Delayed

be caused by lack of AHF or Christmas factor, as the coagulation defect disappears after the addition of barium sulphate absorbed plasma as well as serum. In addition, the patient's plasma makes the thromboplastic activity in a plasma sample with combined defects normal (lack of AHF and Christmas factor).

The main problem is whether it is a case of PTA deficiency. *Frick and Hagen* mention that Hageman plasma cannot correct the coagulation defect in plasma with PTA deficiency. *Ramot, Singer, Heller and Zimmerman* found that the addition of plasma from a patient with PTA deficiency to Hageman plasma made the thromboplastic activity normal. The PTA factor is partly absorbed by barium sulphate and partly destroyed by heating. It seems improbable that there is a PTA factor left in a serum sample which is absorbed twice and heated to 56°C during 30 min.

We have tried the applied test serum on plasma samples from patients with known PTA deficiency (*Sjölin*, to be published) and it did not correct this coagulation defect. According to our results we must conclude that our patient lacks the Hageman factor. The freezing experiments demonstrated that the coagulation defect disappeared after the patient's plasma had been stored with its normal content of platelets. This phenomenon has been described before in man (*Sjölin* [1956]) and in the horse (*Sjölin* [1957]). The problems concerning the effect of freezing the plasma need further

investigation. When it has been postulated that patients with the Hageman trait do not need blood transfusion before surgical treatment (*Ramot, Singer, Heller and Zimmerman*) it will be necessary to modify this statement. It seems only of value, if the patients do not have clinical symptoms of a tendency to bleed. In the plasma of our patient's mother no definite clotting defect could be demonstrated.

The inheritance of the clotting defect in the family described seemed to be sex-linked and recessive as in ordinary haemophilia.

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Summary

A coagulation defect in the plasma from a 1 year old boy with a haemorrhagic diathesis is described. The defect was revealed by the thrombin generation test and seemed to be caused by lack of the Hageman factor. The coagulation defect could be corrected by freezing of the plasma. The patient's maternal grandfather, who died at the age of 48 suffered from haemophilia. In the plasma from the patient's mother no coagulation defect could be demonstrated.

Zusammenfassung

Es wird eine plasmatisch bedingte Störung der Blutgerinnung bei einem 1 Jahr alten Jungen mit hämorrhagischer Diathese beschrieben. Sie wurde durch den Thrombin-Bildungstest aufgedeckt und war offenbar durch Fehlen des Hageman-Faktors verursacht. Durch Einfrieren des Plasmas konnte die Störung behoben werden. Der Grossvater mütterlicherseits des Patienten litt an Hämophilie und starb im Alter von 48 Jahren. In dem Plasma der Mutter konnte kein Gerinnungsdefekt nachgewiesen werden.

Résumé

L'auteur décrit un nouveau défaut de coagulation dans le plasma chez un garçon d'un an atteint d'une diathèse hémorragique. Le défaut a été révélé par le test de la thromboplastinoformation et semble être dû à

l'absence du facteur Hageman. Le défaut de coagulation a pu être corrigé par la congélation du plasma. La grand-mère maternelle du malade, décédée à l'âge de 48 ans, était atteinte d'hémophilie. Dans le plasma de la mère du malade, aucune altération de la coagulation n'a pu être trouvée.

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FURTHER INVESTIGATIONS OF THE GENETIC MECHANISM OF THE HAPTOGLOBINS

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In 1939 *Jayle* (1) made the interesting finding of haemoglobin-binding proteins in human serum; these substances he named haptoglobins. In the years following this discovery, the haptoglobins were studied intensively by various workers (2, 3, 4, 5, 6, 7). A new interest in the subject arose, when *Oliver Smithies* (8, 9) using a new electrophoretic technique, succeeded in discerning between three different patterns of haemoglobin-binding proteins, which he identified with *Jayle's* haptoglobin on account of the common haemoglobin-binding properties and the identical migration by paper electrophoresis. *Smithies* used a starch gel medium in which the migration of some protein molecules seemed to be not only a function of their electrical charge, but also to be related to the size of the molecules, probably because the starch gel functions as a filter, having a pore size about the same diameter as the serum protein molecules.

A theory of the inheritance of the haptoglobins was advanced in 1955 by *Smithies* and *Walker* (10). According to this theory, the serum groups are determined by two autosomal genes with incomplete dominance. A family study comprising 18 families with 37 children showed complete agreement with the genetic theory. Originally the three groups were named I, II A and II B. Of these I and II B represented the homozygous groups, and IIA the heterozygous group. As the identity of the three groups with *Jayle's* haptoglobin seems established, *Smithies* and *Walker* (11) now propose the notation shown in Table 1.

The University Institute of Forensic Medicine in Copenhagen annually performs blood grouping in about 1800 cases of disputed paternity. With

the blood group systems used as a routine the theoretical percentage of exclusion is between 50 and 60. Naturally, the Institute is interested in any method capable of excluding paternity, and so the method developed by *Smithies* was studied with the aim of determining the applicability of the haptoglobin system to paternity cases.

Table 1. Haptoglobin System of the Serum Protein Groups

Old nomenclature	New nomenclature	Genotypes
Group I	Haptoglobin 1-1	Hp ¹ /Hp ¹
Group II A	Haptoglobin 2-1	Hp ² /Hp ¹
Group II B	Haptoglobin 2-2	Hp ² /Hp ²

In a previous paper (12), the author reported the distribution of the haptoglobin groups in 232 unrelated adults, in 53 families with a total of 149 children, in 102 mother-child combinations and in 26 pairs of twins. The figures presented were in agreement with the proposed genetic theory.

Since the publication of the above mentioned figures, the number of observations has increased considerably. A follow-up of the figures earlier presented might therefore now be of value.

Technique

The technique used in the present work is essentially the same as that described by *Smithies* (9): "A starch gel containing the desired buffer is prepared in a suitable plastic tray. The sample is introduced into a vertical slit in the gel at right angles to the greatest length of the gel. Electrical contact is made to the ends of the gel with filter-paper wads, soaked in a suitable buffer solution, which dip into vessels containing the same solution. Filter-paper bridges in turn connect these vessels to the electrode chambers. Current is passed for the required time. The gel is then removed from the tray and sliced along its length in a horizontal plane, and the slices obtained are stained with a protein dye. After washing with dye solvent the stained, separated proteins may be observed."

Plexiglass is also used for our trays to the starch gels. Two different types of trays are used, one with six and one with ten vessels. The width of the vessel of the first type is 20 mm, while the width of the second type is only 10 mm. Depth and length of the vessels are the same for both types of trays, viz. 6.5 mm and 250 mm.

The electrical contacts to the gels are made with filter-paper wads soaked in a buffer solution of about the same pH as the gels. It is not necessary to have wads for each single vessel; wads with a width corresponding to that of the entire tray can be used. The number of layers of filter-paper in the wads must be so great that the voltage loss over the wads is negligible, 4 layers usually suffice.

The bridge solution contains 0.15 mole of H₃BO₃ and 0.03 mole of NaOH/litre.

The electrodes are immersed in 10% NaCl solution.

Fresh bridge and NaCl solutions are prepared each day.

Filter-paper bridges connect the electrode compartments and the bridge solutions.

Coiled silver, $\frac{1}{2}$ mm thick is used for the electrodes.

As a source of power 220 v.d.c. is used, the current being controlled by a 20,000 Ω rheostat in series. The voltage gradient in the starch is measured by a high-resistance voltmeter using silver thread probes inserted next to the filter-paper wads at the end of the vessels. The distance between the two filter-paper wads is 20 cm. During electrophoresis the voltage gradient is kept at approximately 120 volt, i.e. 6 volt/cm, corresponding to a current of 4–5 mA for each gel.

As the heating of the gel during electrophoresis is only about 2°, it is unnecessary to make the gel tray rest on a copper plate to obtain sufficient cooling.

During the electrophoresis the gels are protected from loss of water by evaporation by pouring a layer of mineral oil on the surface after introduction of the sample.

The electrophoresis time selected is 5 hours; after this period the differences of the haptoglobin patterns are most clearly demonstrable.

For introduction of the sample the filter-paper method is used. A transverse cut is made in the gel (for this purpose a ground spatula made of the exterior half of an old tableknife has proved most useful), and a piece of filter-paper cut accurately to match the cross-section of the gel and moistened with serum is introduced into the slit. The nature of the filter-paper is immaterial. One was chosen, which was moistened sufficiently by 50 μ l serum (25 μ l for the small pieces of paper to the narrow vessels). On the same gel two or even three pieces of filter-paper were placed successively in two, or respectively three different slits. Where three transverse sections are made, they were placed approximately 2, 8 and 14 cm from the cathodic end of the vessel.

For the electrophoresis, several different samples of potato starch were supplied by Struer's Chemical Laboratory, Copenhagen. It was possible to make gels applicable for electrophoretic work from all the starch samples supplied. The suitability of the gels for electrophoresis depends primarily upon the degree of hydrolysis of the starch.

The degree of hydrolysis of a starch sample with hydrochloric acid can be varied by changing either the time or the temperature. Longer time or higher temperature means increased hydrolysis. If it is attempted to obtain a suitably hydrolyzed starch by changing either one or the other of these two factors, it is impossible to know beforehand to what extent the chosen factor must be changed. A third method, however, is to keep time and temperature constant and vary the amount of hydrochloric acid added to the starch—acetone—mixture. More hydrochloric acid means increased hydrolysis.

It was noticed that different starch samples needed different amounts of hydrochloric acid to become satisfactorily hydrolyzed. In several consecutive experiments with different starch samples, it was found that if hydrochloric acid is added until the same pH is reached, almost identical quality of all hydrolyzed starch samples is obtainable. A pH of 1.98 yields the most suitable starch for electrophoretic use. If a starch sample is hydrolyzed too little, the hot solution will be too viscous to handle during preparation. If the degree of hydrolysis is too high, the final gel will lack sufficient strength.

Using 45 minutes for the hydrolysis at 38.5° C our present technique of preparing the starch is as follows: A preliminary experiment is carried out, in which 10 gms of starch, 20 ml of acetone and 200 ml of distilled water are mixed. The pH is measured potentiometrically by means of a glass electrode, while 1 N hydrochloric acid is added dropwise until a pH of 1.98 is reached. Normally the pH of the mixture of starch—acetone—water increases slightly (about 0.5) before the hydrochloric acid is added. The change seems

immaterial, however, the influence on the amount of hydrochloric acid needed to change the pH to 1.98 being negligible, probably because the buffer strength of the mixture is small. After preliminary testing of the starch sample a larger quantity is prepared. The calculated amount of 12 N hydro-chloric acid is added to 300 gms of starch mixed with 600 ml of acetone. After 45 minutes in 38.5° C waterbath the process is stopped by 20.4 gms of $\text{CH}_3\text{COONa}/150 \text{ ml H}_2\text{O}$, the starch is washed several times with distilled water in a Büchner funnel, resuspended in water and left overnight at room temperature. The next day the starch is washed in the Büchner funnel, first with the buffer solution used for the preparation of the gels, then with distilled water, and suspended in acetone. After sedimentation of the starch the acetone is decanted, and new acetone is added. After renewed sedimentation of the starch, the acetone is removed on the Büchner funnel, and the starch is spread on a large piece of filter-paper and dried at room temperature. When the smell of acetone has disappeared the starch is considered ready for use. Usually the starch is left to dry for one night, and it is then completely dry the next day. This method is usually an easy way of obtaining usable hydrolyzed starch. Should it happen that a batch is hydrolyzed either too much or too little, it can be remedied by mixing with a batch of starch deliberately hydrolyzed too little or too much as the case may be.

The buffer solution used to make the gel contains 0.015 mole H_3BO_3 and 0.006 mole NaOH/litre . 48 gms of starch and 300 ml of buffer are used for each tray. The mixture is heated over a naked flame in a 500 ml conical flask under constant swirling. Just below boiling point the grains of the starch rupture and a viscous homogenous solution is obtained. The flask is then removed from the flame under continued swirling, after which negative pressure is applied for 10–15 seconds to remove small air bubbles. The hot starch solution is poured into the vessels and covered with a flexible plastic sheet. Excess gel is squeezed out by means of a rigid plastic sheet. After cooling for about 15 minutes the gel is ready for use.

Apparently sera can be stored for years at -20°C without showing changes in the electrophoretic pattern. At $+4^\circ \text{C}$, however, changes may be seen after about a week.

For the deliberate "haemolyzing" haemoglobin to the extent of approximately 300 mg% was added to a fraction of each serum. In this manner a "saturated pattern" of Hp-types will always be obtained.

All sera are examined twice on two consecutive days. On the first day all sera in the family and twin studies are examined unhaemolyzed as well as after addition of human haemoglobin to the extent of approximately 300 mg%, while the sera of the mother-child combinations are only examined after deliberate "haemolyzing". On the second day a control examination is made with haemolyzed sera of all samples only. The sera found to be of type Hp 1-1 are "run" alone, while sera of type Hp 2-2 and Hp 2-1 are tested together with controls of type Hp 2-1 and Hp 2-2 respectively running the test-sample and the control simultaneously on the same gel. Two pieces of filter-paper measuring 6.9 mm are moistened with 25 μl of the serum under examination and the control serum respectively, and placed side by side in the same slit in the gel. Before the staining it is useful to check the unstained gels by placing a white paper under the trays. Normally the sera of Hp 1-1 is clearly demonstrable in this way (the pattern may be blurred when the haemolysis is very strong), but often also the other types can be seen at this stage. Unstained the Hp-types are usually seen most clearly after an electrophoresis period of 3–4 hours. At the first examination all slabs are stained with amidoblack. At the control examination, however, half of the controls are stained with amidoblack, the other half with a benzidine solution. Staining with benzidine has appeared to be of great help in

Fig. 1
The three Hp-types of
unhaemolyzed sera.

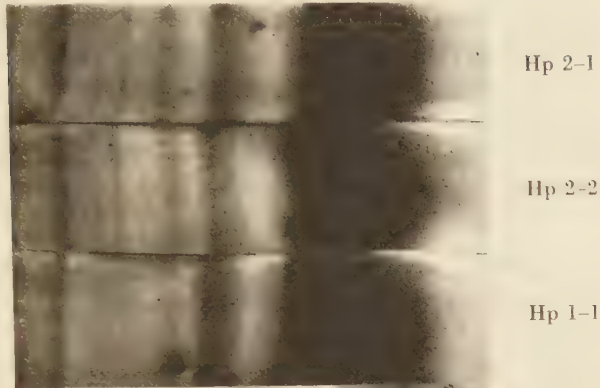


Fig. 2
The three Hp-types after
"saturation" of haptoglobin
with haemoglobin.

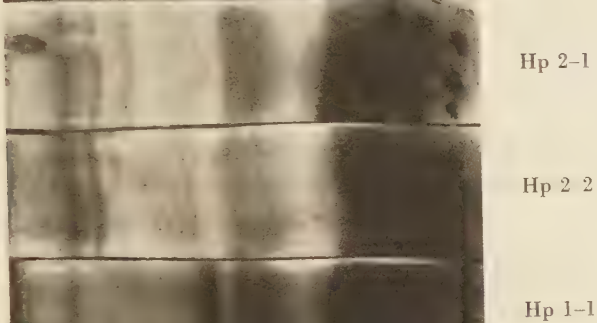
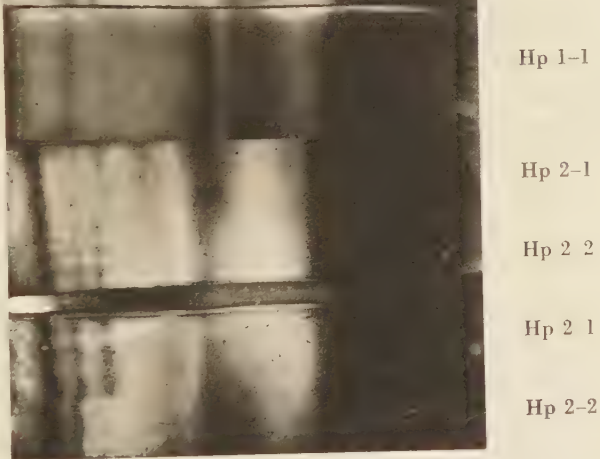


Fig. 3
A "double run" of Hp 2-1
and Hp 2-2 with unhae-
molyzed sera and after
addition of haemoglobin.



determining all three Hp-types when poorly developed. All readings of reactions are done as blind tests, and all results are read independently by two persons.

Results

The investigation comprised sera from 1033 unrelated persons, 106 families with a total of 278 children, 101 pairs of twins, 593 mother-child combinations and 34 newborn infants. The blood samples examined in this

study were grouped according to the A_1A_2BO , MNS, Rh (CDEc), P and *Kell* systems. Examination of the blood type S, however, was not performed in all cases because of a temporary shortage of a suitable anti-S serum. Further, the families were grouped according to the *Duffy*-system (Fy[a]) and 70 of the families according to the *Kidd*-system (Jk[a]), too. The following figures include the results previously published (12).

Table 2. Hp-Groups of 1033 Sera from Unrelated Adult Males and Females

Type	Males			Females			Total Males and Females	
	obs.	exp.	χ^2	obs.	exp.	χ^2	number	%
Hp 1-1	42	40	0.1000	133	135	0.0296	175	16.9
Hp 2-2	88	86	0.0465	287	289	0.0138	375	36.3
Hp 2-1	108	111	0.0811	375	372	0.0242	483	46.8
Totals	238	237	0.2276	795	796	0.0676	1033	100

$\chi^2 = 0.295$ (for 2 d.f., $p = 0.9$ to 0.8)

In Table 2 the Hp-groups of 1033 sera from unrelated adults are recorded. As the difference in the sexual distribution of the haptoglobin-types is not significant, the pooled figures for males and females are used for the calculation of the gene frequencies:

$$Hp^1 = 0.169 + \frac{0.468}{2} = 0.403$$

$$Hp^2 = 0.363 + \frac{0.468}{2} = 0.597$$

Accordingly, the distribution of the phenotypes is as follows:

$$Hp\ 1-1 = 0.403^2 = 0.1624$$

$$Hp\ 2-2 = 0.597^2 = 0.3564$$

$$Hp\ 2-1 = 2 \times 0.403 \times 0.597 = 0.4812$$

$$1.0000$$

The relationship between observed and expected frequencies is shown in Table 3. The differences are insignificant.

Families

So far 106 families with a total of 278 children were examined (Table 4). In 26 families, where both parents were homozygous, only 1 Hp-type was

Table 3. Observed and Expected Frequencies of Hp-Types

Type	obs.	exp.	χ^2
Hp 1-1	175	168	0.351
Hp 2-2	375	368	0.136
Hp 2-1	483	497	0.396
	1033	1033	0.883
			(for 1 d.f., $p = 0.4$ to 0.3)

theoretically possible in the children. 61 children in these families showed no exception from the hypothesis. In 58 families, one parent was homozygous, the other heterozygous. In the 159 children no instance of homozygosity incompatible with the homozygous parent was encountered. The differences between expected and observed distribution of the Hp-type in the offspring of 2 heterozygous parents as well as of the combination of a homozygous and heterozygous parent were insignificant.

In 8 children (not included in Table 4) it was not possible to determine the Hp-type, apparently because this special protein fraction was absent,

Table 4. Haptoglobin Types of Family Material

Type	Parents			Children					
	number		χ^2	Hp 1-1		Hp 2-1		Hp 2-2	
	obs.	exp.		obs.	exp.	obs.	exp.	obs.	exp.
Hp 1-1 + Hp 1-1	4	2.6	0.754	7	7	—	—	—	—
Hp 1-1 + Hp 2-1	15	15.5	0.016	20	19.5	19	19.5	—	—
Hp 1-1 + Hp 2-2	13	11.6	0.169	—	—	29	29	—	—
Hp 2-2 + Hp 2-1	43	34.1	2.323	—	—	64	60	56	60 †
Hp 2-2 + Hp 2-2	9	12.7	1.078	—	—	—	—	25	25 †
Hp 2-1 + Hp 2-1 ¹	22	22.8	0.028	10	12.5	26	25	14	12.5

4.368

(for 5 d.f., $p = 0.5$ to 0.3)† $\chi^2 = 0.533$ (for 1 d.f., $p = 0.5$ to 0.3)‡ $\chi^2 = 0.680$ (for 2 d.f., $p = 0.8$ to 0.7)

¹ One child of Hp-type 1-1 has been excluded from the results on account of probable illegitimacy being excluded by the Rh-system.

8 children with undeveloped Hp-type are not included in table 4 (cf. table 5).

the sera presenting a pattern identical with that most often found in the newborn. These sera were found unchanged at a repeated examination about 6 months later. At the renewed withdrawal of blood from these children the parents were asked whether the children had had any diseases; all answers were in the negative. The age and sex distribution of the children concerned and the Hp-type of their parents are shown in Table 5.

Table 5. Children with Undeveloped Hp-Types in the Family Material.
Age- and Sex Relations to Parents

Hp 1-1	Parents		Children	
	Hp 2-1	Hp 2-2	Age in years	Sex
mother + father	mother mother + father	mother + father	11	m
		mother + father	11	f
		father	10	m
			15	f
			10	m
	father	mother	11	m
	mother	father	12*	m
			7*	m

* common parents

m = male f = female

At the first examination a boy (aged 10) showed an undeveloped pattern: 6 months later, however, a normally developed haptoglobin pattern (Hp 2-1) was seen.

In 14 children (included in Table 4) the Hp-types were poorly developed and could not be determined with certainty by amidoblack staining. After sprinkling with a benzidine solution the types, which are shown in Table 6, were easily determined.

Twins

Altogether 101 pairs of twins were examined. The results are recorded in Table 7.

Samples from 95 of the twin pairs were put at the disposal of the author by the University Institute of Human Genetics from their series of unselected twins. The poly-symptomatic similarity test including blood grouping was carried out by Dr. *M. Hauge*. The author, when examining the Hp-types of the samples, had no knowledge of the identity of the persons from whom the serum was derived.

Table 6. Children in the Family Material, only Determinable after Benzidine Staining

Sex	Age (years)	Hp Type
m	10	Hp 2-2
f	unknown	Hp 2-2
f	unknown	Hp 2-2
m	17	Hp 2-2
f	10	Hp 2-2
m	10	Hp 2-2
m	12	Hp 2-1
m	9	Hp 2-2 (six months later normally developed Hp-type)
m	12	Hp 2-2 } common parents
f	13	Hp 2-2 }
m	8	Hp 2-2 } six months earlier undeveloped
m	9	Hp 2-2 }
m	9	Hp 2-2 }
m	6	Hp 2-2 }

m = male f = female

Table 7. The Hp-Type of 101 Pairs of Twins

	Different Hp-types	Identical Hp-types
Monozygotic pairs*	0	55 Hp 1-1:8 Hp 2-2:24 Hp 2-1:23
Dizygotic pairs, like-sexed*	17	29
Total	17	84

* The zygotic diagnosis was established by means of the polysymptomatic similarity test including in all cases the ABO, MNS, Rh (CDEc), P, Kell, Duffy and Lutheran blood groups, and in some cases supplemented by the Lewis and/or Kidd groups.

Mother-child combinations (not including family study):

Sera from 593 mother-child combinations were examined. 2 of the mothers showed a pattern identical with that usually seen in newborn infants. They were excluded from the material for the reasons stated below. The distribution of the remaining 591 mother-child combinations is pre-

Table 8. Hp-Types of 591 Mother-Child Combinations

Mother		Child		χ^2
Type	Number	Type	obs. Number exp.	
Hp 1-1	98	Hp 2-1	55 54.9	0.002
		Hp 1-1	37 37.1	0.003
		undev.	6	$\Sigma = 0.005$ for 1 d.f., $p = 0.990$ to 0.995
Hp 2-2	209	Hp 2-1	66 72.9	0.65
		Hp 2-2	115 108.1	0.44
		undev.	28	$\Sigma = 1.09$ for 1 d.f., $p = 0.3$ to 0.2
Hp 2-1	284	Hp 2-2	70 77.3	0.69
		Hp 2-1	137 129.5	0.43
		Hp 1-1	52 52.2	0.00
		undev.	25	$\Sigma = 1.12$ for 2 d.f., $p = 0.6$ to 0.5
	591	591	532	Total $\chi^2 = 2.21$ for 4 d.f., $p = 0.7$ to 0.6

sented in Table 8. The expected frequency of the children was calculated on the assumption that the undeveloped infants were evenly distributed among the three phenotypes.

In 83 mother-child combinations, the electrophoresis was repeated at a later date on a new sample of serum obtained by renewed withdrawal of blood. As far as the mothers were concerned there was complete agreement between the results of the first and second examinations. At the first examination 63 of the children were well developed, 11 poorly developed but determinable, and 9 undeveloped. At the second examination the 63 children showed complete agreement between the first and second examinations, the 11 were now better developed, and the remaining 9 were determinable (Table 9).

A large percentage of the infants had not developed a determinable haptoglobin pattern within the first months of life (Table 10).

In the age group 1-2 months 52% were undeveloped. From 2-4 months the percentage was 13, and from 4-6 months only about 3. In the group

Table 9. Children Undeterminable at First Examination, but Determinable at Second Examination

Sex	Age (Exam. I)	Age (Exam. II)	Hp-type
m	6 weeks	13 weeks	Hp 2-2
m	7 weeks	*18 weeks	Hp 2-1
f	11 weeks	14 weeks	Hp 2-2
m	7 weeks	15 weeks	Hp 2-1
f	9 weeks	16 weeks	Hp 2-2
m	5 weeks	13 weeks	Hp 2-2
m	6 weeks	13 weeks	Hp 1-1
m	7 weeks	11 weeks	Hp 1-1
m	5 weeks	8 weeks	Hp 2-1

m = male f = female

* Also examined when 10 weeks old: undeveloped

Table 10. Percentage of Undeveloped Children in Relation to Age

Months	Total	Number of undeveloped	% of undeveloped
1-2	71	37	52
2-4	147	19	13
4-6	104	3	3

aged over 6 months about 3% were undeveloped. This agrees very well with the finding that 3.4% of children of undeveloped Hp-type were among the 278 children in the family study where the youngest child was aged three. 525 of the 591 children in the mother-child study were determinable, 25 only by means of benzidine, while amidoblack staining gave unreliable results in these cases.

Newborn infants

An investigation of sera from newborn infants was started recently. Sera from 34 newborn infants (blood withdrawn from the umbilical cord) have been examined so far. The results of this preliminary investigation are shown in Table 11.

Among the 34 newborn infants the Hp-type was determinable in 4 children. 2 of the 4 infants with determinable Hp-type were tested by

repeated examination 8 days later (capillary blood from the heel) and showed unchanged haptoglobin-pattern. Of the 30 infants who were undeveloped at the first examination 10 were tested again 8 days later. By the second examination 6 of those were determinable (4 only by means of benzidine staining), and 4 were still undeveloped.

Table 11. Development of Hp-types at Birth and 8 Days Later

Sex	Child		Mother
	Newborn	8 days later	
m	Hp 1-1	Hp 1-1	
f	Hp 2-2	Hp 2-2	Hp 2-1
m	Hp 2-2	not repeated	Hp 2-1
m	Hp 2-1	not repeated	Hp 2-2
f	Undev.	Hp 1-1	
m	Undev.	Hp 2-1 (benzidine)	
m	Undev.	Hp 2-2	
f	Undev.	Hp 2-1 (benzidine)	
m	Undev.	Hp 1-1 (benzidine)	
f	Undev.	Hp 2-1 (benzidine)	
m	Undev.	Undev.	
m	Undev.	Undev.	
m	Undev.	Undev.	
f	Undev.	Undev.	
14			
20	Undev.	not repeated	
Total 34		m = male f = female	

Discussion

Reliability of the method

Sera from 83 mother-child combinations plus several other persons were examined repeatedly. There was complete agreement between the results of the first and second examinations except in some of the children who showed undeveloped or poorly developed Hp-types at the first examination but determinable respectively more distinct Hp-types at the second examination.

The distribution of observed Hp-types was in good agreement with the expected figures.

If sera are stored for more than one week at room temperature or even at $+4^{\circ}$, the characteristic haptoglobin-pattern may disappear. But ageing phenomena or infection of a serum have never caused erroneous interpretations of the electrophoretic pattern.

On the basis of these facts the method may be regarded with confidence.

Problems of sera with undeveloped Hp-type

At an early stage of the study it was noticed that the Hp-types of many infants were poorly developed or undeveloped. In the course of the study, however, poorly developed or even undeveloped Hp-types were found also among older children or even adults.

A systematic investigation of the adult sera with poorly developed Hp-type was not performed, but it is the author's impression that the poor development of the Hp-types observed in some adults is a permanent phenomenon in these persons.

A relatively small percentage of the individuals examined showed undeveloped Hp-types. In newborn infants a well established haptoglobin pattern was an exception. Already at the age of one week the number of determinable Hp-types seemed to be considerably increased and above the age of 4 months an undeveloped Hp-type was a rare exception.

Theoretically, the few exceptions with determinable Hp-types among the newborn infants might be due to passage of the maternal haptoglobin to the infant during pregnancy. Apparently that is not the case, as determinable infants had a Hp-type different from that of the mother (Table 11). In most cases the failing development of the haptoglobins seems to be ascribable to the age of the individual, but it is possible that disease may play a rôle in some cases—that question is now being investigated. However, according to the parents, the 8 children with undeveloped Hp-types in the family study were all in good health.

Forensic aspects of sera with undeveloped Hp-type

In a genetic system like the present a serious cause of erroneous paternity exclusion is the existence of a third, silent allele. In the mother-child study two mothers (excluded from Table 8) with undeveloped pattern of haptoglobin were found. It has not been possible so far to obtain new blood

samples or information about possible diseases. However, their pattern or rather lack of pattern might be due to homozygosity with regard to a third allele. The children, however, of both mothers were of type Hp 2-1, which appears to exclude this possibility. Further, a silent gene capable of producing 2 homozygotes within a group of 593 persons would be expected to show up as apparent mother-child exclusions, which have not been observed.

Evaluation of the study with respect to forensic medicine

The family study fully confirms the proposed theory of the genetic mechanism. However, from a medico-legal point of view a mother-child material is essential to estimate the probability of a "silent allele" causing false exclusions of paternity. If such an allele (designated x) is rare, the probability of demonstrating it by apparent mother-child exclusion is with good approximation: $2 \cdot \text{Hp}^1 \cdot \text{Hp}^2 \cdot x = 2 \cdot 0.403 \cdot 0.597 \cdot x = 0.4811 \cdot x$. Presuming that the distribution of possible mother-child exclusions due to x is a Poisson distribution, the upper limit of their frequency based upon 600 mother-child combinations will be about 0.01, if a confidence limit of 95% is used. This corresponds to an upper limit of the frequency of a hypothetical "silent allele" of about 0.02. Exclusion of paternity based on "incompatible homozygosity" in man and child may consequently be estimated to be of a reliability of about 99% (with the above mentioned confidence limit of 95%).

Relation to blood groups

No obvious relationship was found between the Hp-types and any of the blood groups used in the study. Analysis of a possible linkage between the Hp-types and some of the blood groups is contemplated but has not yet been carried out.

Conclusion

In the author's view the Hp-system, based on the data collected, may now be of valuable help in genetical investigations. At the Danish Institute of Forensic Medicine the electrophoretic examination of sera in paternity cases will henceforth be used on an increasing scale.

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Summary

Further results of a study on the genetic mechanism of the haptoglobins are presented. The observations on unrelated persons, families, twins and mother-child combinations, which are recorded in tables, fully confirm the theory that the haptoglobins are controlled by two autosomal genes with incomplete dominance. The gene frequencies are calculated to $Hp^1:0.403$ and $Hp^2:0.597$. The technique is described, with special emphasis on the preparation of the starch gel. The observations comprise 1033 unrelated persons, 106 families with a total of 278 children, 101 pairs of twins, 593 mother-child combinations, and 34 newborn infants. The different aspects of the investigation are discussed, especially with regard to the reliability of exclusions of paternity.

It is concluded that the Hp -types may now be of use as valuable evidence in cases of disputed paternity.

Zusammenfassung

Es werden weitere Ergebnisse einer Untersuchung über den Erbgang der Haptoglobine vorgelegt. Die Beobachtungen an nicht verwandten Personen, Familien, Zwillingen und Mutter-Kind-Kombinationen werden in Tabellen zusammengefaßt; sie bestätigen vollauf die Theorie, daß die Haptoglobine durch zwei unvollständig dominante, autosomale Allele kontrolliert werden. Folgende Genhäufigkeiten werden berechnet: $Hp^1: 0,403$, $Hp^2: 0,597$. Die Untersuchungstechnik wird beschrieben, wobei die Herstellung des Stärkegels besonders berücksichtigt wird. Bisher wurden 1033 nicht verwandte Personen, 106 Familien mit insgesamt 278 Kindern, 101 Zwillingspaare, 593 Mutter-Kind-Kombinationen und 34 neugeborene Kinder untersucht. Die verschiedenen Gesichtspunkte dieses Forschungsprogrammes werden diskutiert, wobei das Problem der Zuverlässigkeit von Vaterschaftsausschlüssen besonders betont wird.

Es ergibt sich, daß die Hp -Typen jetzt in Fällen umstrittener Vaterschaft wertvolle Information bieten können.

Résumé

Il s'agit d'une nouvelle étude sur le mécanisme général des haptoglobines. Les observations faites sur des individus isolés, sur des familles, sur des jumeaux et sur des enfants et leur mère, qui sont réunis dans des tableaux, confirment entièrement la théorie que les haptoglobines sont contrôlées par deux gènes autosomiaux, ayant une dominance incomplète. Le calcul de la fréquence de ces gènes est le suivant: $Hp^1:0,403$ et $Hp^2:0,597$. La technique est décrite en insistant spécialement sur la préparation du «starch gel». Les observations concernent 1033 personnes isolées, 106 familles avec 278 enfants, 101 jumeaux, 593 enfants avec leur mère et 34 nouveau-nés. Les différents points des recherches sont discutés, en particulier en ce qui concerne la certitude d'exclusion de la paternité. L'auteur conclut que les types Hp ont une réelle valeur en cas de doutes sur la paternité.

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DIE EUGENISCHE BERATUNG BEIM RETINOBLASTOM (GLIOMA RETINAE)

Von FRIEDRICH VOGEL

I. Einleitung und Problemstellung

Wenn die Genetik eines krankhaften Merkmals aufgeklärt ist, so muß man die praktisch-eugenischen Schlüsse ziehen. Bedingt das Merkmal eine schwere Erkrankung oder Mißbildung, dann ist es das Ziel der Eugenik, auf Grund genetischer Einsicht seinem Auftreten nach Möglichkeit vorzubeugen. Unter den augenblicklichen Bedingungen gibt es hier zwei Wege: Die Konzeptionsverhütung und die freiwillige Sterilisierung aus eugenischer Indikation. Für den zweiten Weg ist die Rechtslage in den deutschen Ländern verschieden und bislang noch meistens mehr oder weniger ungeklärt (Nachtsheim 1952, 1956). Bevor der Arzt eine Sterilisierung aus eugenischer Indikation durchführt, sollte er im eigenen Interesse das Gutachten eines anerkannten Erbbiologen einholen.

Die eugenische Beratung in bezug auf die Konzeptionsverhütung dagegen wird vom Arzt und besonders vom Ophthalmologen recht oft erwartet, und er kann sie auch selbständig durchführen, wenn ein Merkmal genetisch einwandfrei geklärt ist.

Neuerdings gehört das Retinoblastom zu diesen Merkmalen. Bekanntlich führt dieser sehr bösartige Tumor oft zum Tode oder zur Erblindung im Kindesalter; eine geeignete Vorbeugung durch eugenische Beratung liegt also im Interesse des Einzelnen wie der Allgemeinheit.

Auf der anderen Seite sind die genetischen Verhältnisse nicht ganz einfach, und der nicht speziell auf dem Gebiet der Genetik Ausgebildete läuft Gefahr, bei der Beratung Fehler in der einen oder der anderen Richtung

zu begehen. Das rechtfertigt vielleicht eine etwas detailliertere Diskussion der verschiedenen konkreten Fälle.

Kürzlich faßten wir, was über die Genetik des R. bekannt ist, folgendermaßen zusammen (Vogel 1957):

«Das R. kommt in einer erblichen und einer nichterblichen Form (Phäno kopie) vor. Für die erbliche Form ist ein autosomal-dominantes Gen mit unvollständiger Penetranz verantwortlich. 60% der erblichen Fälle sind doppel seitig, 40% einseitig. Die Penetranz liegt durchschnittlich bei etwa 80%; sie schwankt jedoch parallel zur Expressivität etwas von Familie zu Familie. Das R.-Gen ist einer ziemlich erheblichen Selektion unterworfen. In der Bevölkerung hat sich ein Gleichgewicht zwischen Selektion und Mutation eingestellt, was zur Folge hat, daß relativ viele erbliche R.-Fälle sporadisch, als dominante Neumutationen auftreten...

Quantitative Betrachtungen über den Selektionswert des R.-Gens und Untersuchungen an der Nachkommenschaft geheilter R.-Patienten führen jedoch übereinstimmend zu dem Ergebnis, daß nur eine Minderzahl der sporadischen R.-Fälle als Neumutanten anzusehen ist. Unter den einseitigen beträgt ihre Anzahl etwa 10–20%, bei den doppel seitigen liegt sie zwischen 50 und 100%.»

II. Die eugenischen Konsequenzen für die Familie

Daraus lassen sich nun die eugenischen Konsequenzen für die einzelnen möglichen Situationen ableiten.

1. Wir betrachten zunächst die Beratung in der Familie, in der das R. mehrfach vorgekommen ist.

a) Der Fragende war selbst an R. (einseitig oder doppel seitig) erkrankt, ein Elternteil war ebenfalls befallen.

Damit ist erwiesen, daß der Fragende an der dominant erblichen Form litt. Jedes seiner Kinder hätte somit die Chance von 40% (1:1-Verhältnis bei dominantem Erbgang und 80% Penetranz), an R. zu erkranken. Von einer Fortpflanzung ist dringend abzuraten, ob schon Kinder vorhanden sind oder nicht.

b) Der Fragende war selbst an R. erkrankt, ebenso wie eines oder mehrere seiner Geschwister. Die Eltern waren beide gesund.

Durch die Erkrankung der Geschwister ist erwiesen, daß die erbliche Form vorliegt. Jedes Kind hat deshalb die Chance von 40%, zu erkranken. Von einer Fortpflanzung ist dringend abzuraten.

c) Der Fragende war selbst erkrankt, seine Eltern und Geschwister waren gesund; es sind aber andere Verwandte erkrankt, etwa Großeltern, Geschwister der Eltern usw.

Auch hier liegt die erbliche Form vor, wenn sich das Gen auch bei einem oder einigen seiner Träger nicht manifestiert hat. Wir sahen ja, daß die Penetranz nur 80% beträgt.

Auch hier hätte jedes Kind die Chance von etwa 40%, zu erkranken. Von einer Fortpflanzung ist abzuraten.

Das Gleiche gilt, wenn sich die oben genannten Fälle kombinieren, wenn etwa ein Elternteil und Geschwister befallen sind usw.

d) Der Fragende ist selbst gesund. Es sind aber mehrere unmittelbare Familienangehörige erkrankt, etwa ein Elternteil und ein Geschwister.

Zwei Möglichkeiten gibt es: Entweder der Fragende hat von seinem das Gen tragenden Elternteil das gesunde Allel bekommen, oder er trägt das R.-Gen, das sich nicht manifestierte. Das erste ist bei 50%, das zweite bei 10%, aller gesunden Kinder der Fall. Der Fragende hat also eine Chance

von $\frac{50}{50+10} = 83,3\%$, vom R.-Gen frei zu sein. Dann sind alle seine Kinder mit Sicherheit gesund. Ist er Genträger, wofür die Chance 16,7% beträgt, dann hat jedes seiner Kinder die Chance von 40%, Merkmalsträger zu werden. Insgesamt hat also jedes Kind die Chance $16,6\% \times 40\% = 6,52\%$, an R. zu erkranken.

Das ist unseres Erachtens kein Grund, von der Fortpflanzung abzuraten, wenn man auch auf diese Gefahr hinweisen sollte. Dazu kommt: Mit jedem gesunden Kind wächst die Wahrscheinlichkeit, daß der Fragende wirklich von dem R.-Gen frei ist, und damit die Aussicht für die weiteren Kinder, gesund zu bleiben (vgl. Statist. Anhang 1).

2. Nun gehen wir zur Beratung bei den sporadischen R.-Fällen über, bei denen bisher noch kein weiterer Fall in der Familie vorgekommen ist.

a) Der Fragende war selbst an einem einseitigen R. erkrankt. Kein weiterer Fall in der Familie. Soll er Kinder haben?

Nach unseren Ergebnissen (Vogel 1957) sind zwischen 10 und 20% der sporadischen, einseitigen Fälle dominante Neumutanten. Jedes ihrer Kinder hat eine Chance von 40%, an R. zu erkranken. 80–90% sind Phänokopien; ihre Kinder bleiben gesund. Da wir diese beiden Gruppen aber nicht unterscheiden können, also nicht wissen, zu welcher der Fragende gehört, ergibt sich eine Chance von 5–10%, ein befallenes Kind zu bekommen.

Unseres Erachtens bietet diese geringe Chance keine ausreichende Handhabe, um von einer Fortpflanzung abzuraten. Immerhin wird man den Fragenden auf die Gefahr aufmerksam machen. – Die Chance, zur Gruppe

der nichterblichen Fälle zu gehören, steigt mit jedem gesund bleibenden Kind an (vgl. Statist. Anhang 1).

b) Der Fragende war selbst an doppelseitigem R. erkrankt. Keine weiteren Erkrankungen in der Familie.

Hier ist die Lage viel ernster: Zwischen 50 und 100% aller sporadischen, doppelseitigen R.-Fälle sind dominante Neumutanten. 20–40% ihrer Kinder werden demnach ebenfalls erkranken.

Dieser Prozentsatz reicht unseres Erachtens aus, um von einer Fortpflanzung dringend abzuraten. Ganz besonders muß man davor warnen, daß aus der Ehe zweier R.-Blinder Kinder hervorgehen. Denn mit hoher Wahrscheinlichkeit werden beide Heterozygote des R.-Gens sein; aus ihrer Verbindung sind daher Kranke und Gesunde im Verhältnis von annähernd 3:1 zu erwarten.¹

c) Der Fragende ist selbst ein sporadischer Fall. Er hat aber schon ein an R. erkranktes Kind. Wie sind die Aussichten für weitere Kinder?

Durch die Erkrankung eines Kindes ist erwiesen, daß der Fragende selbst das R. auf Grund einer dominanten Neumutation hat. Alle seine Kinder haben demnach die Chance von 40%, zu erkranken. Von weiteren Kindern muß dringend abgeraten werden.

d) Der Fragende ist wie alle seine Angehörigen gesund. Eines seiner Kinder ist an R. erkrankt. Darf er weitere Kinder haben?

Es handelt sich bei dem Kind mit überwiegender Wahrscheinlichkeit entweder um eine Neumutation, oder um eine Phänokopie. In beiden Fällen ist es sehr unwahrscheinlich, daß weitere Kinder ebenfalls erkranken. Allerdings muß auch mit der Möglichkeit gerechnet werden, daß ein Elternteil das Gen trägt, daß aber die Manifestation ausblieb. Dann hätte jedes Kind eine Erkrankungschance von 40%. Wie wir nach der Theorie erwarten würden, so zeigt jedoch auch die praktische Erfahrung, daß dieser Fall sehr selten ist: Nach *Kaelin* (1955) waren von 959 Geschwistern sporadischer Fälle nur 13 (1,36%) an R. erkrankt.

Man wird den Fragenden auf diese geringe Gefahr aufmerksam machen; von der Fortpflanzung braucht man deshalb nicht abzuraten.

e) Der Fragende ist selbst gesund, keiner seiner Angehörigen trägt das Merkmal, mindestens 2 seiner Kinder aber haben ein R.²

Damit ist praktisch sicher, daß einer der Eltern das Gen in nicht manifestierter Form trägt; jedes weitere Kind hätte die Chance von 40%, zu erkranken.

¹ Abgesehen davon, daß wir nicht wissen, wie die Homozygoten beschaffen sind. Es kann durchaus sein, daß sie irgendwie schwer mißbildet sind.

² Eineiige Zwillinge müssen hier als ein Kind gerechnet werden.

III. Die Auswirkungen der Therapieerfolge beim R. auf die Häufigkeit des Tumors in der Bevölkerung

Im Laufe weniger Generationen ist es den Ophthalmologen gelungen, mit Hilfe der Operation und der Strahlentherapie die früher praktisch infaste Prognose ganz wesentlich zu bessern, so daß heute das R. zu den bösartigen Tumoren mit der günstigsten Prognose quoad vitam gehört. Da aber ein nicht unbeträchtlicher Teil der Fälle, wie wir sahen, erblich ist, muß das eine Erhöhung der Merkmalshäufigkeit in der Bevölkerung zur Folge haben (vgl. Statist. Anhang 2). Nehmen wir zum Beispiel an, der Selektionswert gehe von vollständiger Selektion ($s = 1$) auf $s = 0,2$ bei den einseitigen und $s = 0,5$ bei den doppelseitigen Fällen zurück! Nach den neuesten therapeutischen Statistiken (vg. Dollfus 1953) liegt das durchaus im Bereich des Möglichen. – Dann wird die Zahl der Merkmalsträger innerhalb weniger Generationen sich zirka auf das $1\frac{1}{2}$ fache vermehren; die Zahl der erblichen Fälle wird sich verdoppeln bis verdreifachen. Diese Betrachtung zeigt, daß die eugenische Beratung beim R. nicht nur im Interesse der Betroffenen, sondern auch im dringenden Interesse der Gesellschaft liegt. Führt man sie dagegen so durch, wie hier vorgeschlagen wurde, und gelingt es, in allen genannten Fällen eine Fortpflanzung zu verhindern, so wird sich das R. nur unbedeutend vermehren.

Da das R. ein sehr schweres und eingreifendes Leiden ist, würden wir in den Fällen, bei denen wir von einer Fortpflanzung abraten, auch eine freiwillige Sterilisierung aus eugenischer Indikation befürworten (mit Ausnahme des Falles gesunder Eltern mit mehreren erkrankten Kindern. Hier ist nicht bekannt, welcher Elternteil das Gen trägt. Eine Sterilisierung kommt unseres Erachtens in Frage, wenn ein Elternteil etwa aus der Verbindung mit mehr als einem Partner kranke Kinder hat). Leider verbietet die in Deutschland bestehende Rechtsunsicherheit auf diesem Gebiet noch eine Durchführung in größerem Rahmen, wenn auch einzelne Fälle anderer Erbkrankheiten in den letzten Jahren in Berlin aus eugenischer Indikation sterilisiert wurden (Nachtsheim 1956).

Statistischer Anhang I

Frage: Wie groß ist die Wahrscheinlichkeit, daß eine gesunde Person frei von dem R.-Gen bzw. Träger des R.-Gens, jedoch ohne Manifestation, ist?

Wir sahen, daß von allen gesunden Geschwistern $\frac{50}{50+10} = 83,3\%$

vom R.-Gen frei sind. Das Verhältnis der Genträger zu den Genfreien, die relative Wahrscheinlichkeit, das Gen zu tragen, nennen wir p_0G . Sie beträgt: $\frac{1}{5}$. Dieser Wert ändert sich nun, wenn gesunde Kinder vorhanden sind. (Erkrankt dagegen ein Kind, so ist damit sicher, daß der Patient selbst Genträger war.)¹ Wir berücksichtigen das, indem wir p_0G mit der Wahrscheinlichkeit kombinieren, daß ein Genträger ein bzw. mehrere gesunde Kinder hat. Sie lautet für ein gesundes Kind:

$$p_1G = 0,6$$

Für jedes weitere gesunde Kind gilt die gleiche Beziehung. Daraus ergibt sich für n gesunde Kinder:

$$(1) \quad p_nG = (p_1G)^n$$

Für die gesamte relative Wahrscheinlichkeit folgt:

$$(2) \quad pG = p_0G \times (p_1G)^n$$

und die Wahrscheinlichkeit, Genträger zu sein:

$$(3) \quad P = pG/(1+pG).$$

Diese Betrachtung kann man bei Bedarf noch verfeinern, indem man die Wahrscheinlichkeiten p_1G, \dots, p_nG korrigiert unter Berücksichtigung der Altersverteilung der Merkmalseintritte, wenn die Kinder die Gefährdungszeit noch nicht überstanden haben. Man braucht dann nur mit der Wahrscheinlichkeit, daß die Erkrankung bei dem Alter des Kindes schon eingetreten ist, wenn es überhaupt erkrankt, zu multiplizieren.

Der gleiche Gedankengang trifft mutatis mutandis auch für die Beurteilung der einseitigen sporadischen Fälle mit gesunden Kindern (Fall 2a) zu.

Statistischer Anhang 2

(μ = Mutationsrate des R.-Gens,

s = Selektionsnachteil der Merkmalsträger gegenüber dem Bevölkerungsdurchschnitt

X_0 = Häufigkeit der erblichen Fälle in der Bevölkerung zu Beginn

X_n = Neuer Gleichgewichtswert für die Häufigkeit der erblichen Fälle in der Bevölkerung nach Rückgang der Selektion).

¹ Wenn wir einmal von der Möglichkeit einer unabhängigen Neumutation absehen.

a) Ursprüngliches Verhältnis: Kein Merkmalsträger überlebt. Häufigkeit der erblichen Fälle in der Bevölkerung:^{1) 2)}

$$X_0 = 2\mu$$

b) In einer Generation sei der Selektionswert für einseitige Fälle auf $s_E = 0,2$,
für doppelseitige Fälle auf

$$s_D = 0,5$$

gesunken. 60% aller erblichen Fälle sind doppelseitig, 40% einseitig. Somit beträgt der Gesamtselektionswert:

$$s = s_E \times 0,4 + s_D \times 0,6 = 0,2 \times 0,4 + 0,5 \times 0,6 = 0,38.$$

Der neue Gleichgewichtswert für X ist die Summe der geometrischen Reihe mit dem Anfangsglied $X_0 = 2\mu$ und dem Faktor $(1-s)$. Es gilt:

$$X_n = \frac{X_0}{1-(1-s)} = \frac{X_0}{s}$$

Für das R.-Gen:

$$X_n = \frac{X_0}{0,38} = 2,63 \times X_0$$

Berücksichtigen wir, daß von allen sporadischen R.-Fällen nur (geschätzt) zirka 36,25% Neumutationen sind, für die diese Betrachtung zutrifft, und nehmen wir an, daß die Zahl der Phänokopien im Laufe der Generationen gleichbleibt, so ergibt sich folgende Gesamtzahl von R.-Fällen nach Einspielen des neuen Gleichgewichtes:

63,75% (Phänokopien) + $2,63 \times 36,25\%$ (Erbliche Fälle) = 159,09% der Merkmalshäufigkeit vor Nachlassen der Selektion.

c) Dieses neue Gleichgewicht spielt sich relativ schnell ein. In unserem Beispiel findet sich bereits in der 5. Generation nach dem Nachlassen der Selektion:

$$X_5 = X_0 (1 + 0,62 + 0,62^2 + 0,62^3 + 0,62^4 + 0,62^5) = 2,48 X_0.$$

Zusammenfassung

Da die Genetik des Retinoblastoms jetzt in den wesentlichen Zügen

¹ Der Einfachheit halber sind die Homozygoten des R.-Gens, die Rückmutationsrate und der Faktor $(1-p)$ bei der Mutationsrate vernachlässigt, was bei einem seltenen Merkmal ohne weiteres möglich ist. Ferner ist vernachlässigt, daß der Selektionswert des Gens wegen der Fälle, bei denen die Manifestation unterbleibt, und wegen der wenigen Spontanheilungen auch ohne Therapie nicht ganz 1 ist.

² Der Faktor 2 muß eingesetzt werden, weil die Mutationsrate/Gen angegeben ist, jeder Mensch aber 2 Gene für den R.-locus hat.

aufgeklärt ist, lassen sich die eugenischen Schlußfolgerungen für die Familie und die Bevölkerung ableiten. Es wird dargestellt, in welchen Fällen man von einer Fortpflanzung abraten sollte und wann eine freiwillige Sterilisierung aus eugenischer Indikation angezeigt erscheint. Die zu erwartende Vermehrung der Retinoblastom-Kranken in der Bevölkerung infolge der therapeutischen Erfolge wird untersucht.

Resumé

Etant donné que la génétique du rétinoblastome est actuellement en grande partie connue, les conséquences eugéniques pour la famille et la population peuvent être établies. L'auteur montre dans quel cas il faut déconseiller la procréation et quand une stérilisation volontaire est indiquée. En outre, il examine la probabilité de l'augmentation du rétinoblastome dans la population en rapport avec les succès thérapeutiques.

Summary

The genetics of retinoblastoma have by now been elucidated to such an extent that the eugenic consequences for the family as well as for the population may be explained. The author gives a survey of the cases in which parents should be dissuaded from having children and in which a voluntary sterilization seems to be indicated for eugenic reasons. Further the increase in the number of patients with retinoblastoma, which is to be expected as a consequence of modern therapy, is discussed.

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GENETICS IN INTRACRANIAL TUMOURS

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Our present knowledge of the aetiology and genetic relationships of intracranial tumours is still very limited. Concerning isolated special forms, however, it has been demonstrated that hereditary factors play a considerable part. This holds true for those intracranial tumours which are frequently encountered in *tuberous sclerosis* and *Recklinghausen's disease*; the latter most often in connection with the optic and acoustic nerves. These conditions appear to be dependent on dominant genes, but despite the marked similarity in the pathological anatomical picture, scarcely any genetic connection exists between them (*Borberg*, 1951; *Crowe*, *Schull* and *Neel*, 1956). Whether tumours of the acoustic nerves always represent a manifestation of *Recklinghausen's disease* still remains uncertain.

Hereditary factors play an essential part also with regard to some of the intracranial vascular anomalies; both the cerebral angiomas: *Hippel-Lindau's* and *Sturge-Weber's* syndromes are thus dominant hereditary conditions.

Concerning gliomata and meningiomata, the problem of the etiological significance of the hereditary factors has only been treated in the literature to a limited extent. Recently *Koch* [1954], particularly, has taken up the problem, partly on a basis of previously published causistics and partly from his own investigations. *Koch* is of the opinion that the conclusion may be drawn that gliomata particularly, not infrequently occur familiarly, and he propounded the theory that malignant gliomata, in certain cases,

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develop on a basis of a hereditary determined gliadysplasia demonstrable in the glial tissue outside the tumour itself. The results and conclusions which *Koch* arrived at are, however, only supported to a limited extent by statistical evidence, and therefore the authors of the present paper have considered it of value to attempt to illustrate the question of the heredity of the intracranial tumours by a systematic genetic investigation. In the present paper, the authors account for the results of an investigation of a large proband material of intracranial tumours treated by a slightly modified *Weinberg* technique.

The questions which the authors attempt to elucidate by an investigation of this nature are the following:

- 1) Do intracranial tumours occur more frequently among the relatives of patients with intracranial tumours than in the general population?
- 2) Do intracranial tumours bear any genetic relationship to *Recklinghausen's* disease and *tuberous sclerosis*?
- 3) Have malignant glioblastomata particularly, any genetic relation to other forms of malignant growth and if so, in which form?
- 4) By recording simultaneously epileptic symptoms both in the probands and in their relatives, a possibility exists of illustrating the question of whether epileptic symptoms in patients with organic brain disease are to any extent hereditary. In other words, whether such symptoms occur particularly frequently in patients already predisposed to epilepsy.

Material and Method

All the probands were selected from the Department of Neurosurgery, the University Hospital, Copenhagen, which serves approximately half the population of Denmark. Patients are included only if the diagnosis has been confirmed by histological investigation (specimens from operation or autopsy) and in whom the diagnosis (in all cases) was considered to be established without any doubt. In all, 535 patients with intracranial tumour were included in the proband study. According to the histological findings they were subdivided as follows:

Glioblastomata: All patients between the period 1944-52 are included. A total of 199 cases were concerned. 20 patients, all of whom had died, had to be excluded from the series, in 10 cases because the patient's family could not be traced, in 4 cases no near relatives were alive, one patient was adopted and had no children, and in 5 cases it was not possible to obtain the co-operation of the family. The actual investigation thus comprises 179 cases (124 males and 55 females).

Astrocytomata: During the period 1935-52, 299 patients with histologically verified astrocytoma were encountered. 200 of these were selected at random. In 10 cases, the patient and/or his family could not be traced; 2 patients were of foreign origin, 3 were adopted, 6 had died without surviving near relatives, and 5 refused to co-operate in the investigation. The actual material which was the object of further investigation thus comprises 174 probands (97 males and 77 females). The material investigated does not differ significantly from the total material with regard to sex or age distribution.

Medulloblastomata: In the material from the Department, there were only 39 patients with verified medulloblastoma. Of these, 2 could not be identified, one was a foreigner, and in 9 cases the family refused to cooperate. The actual material thus comprises 27 probands (12 males and 15 females).

Meningiomata: The material from the Department comprises 238 cases of histologically verified meningiomata between the period 1935-52. Out of these, 160 patients were selected at random. They were found not to differ significantly with regard to sex and age distribution from the original material. In 2 cases the patients were adopted, but their own children were included in the investigation. In 2 cases the patients could not be traced and in 3 cases the patients could not be persuaded to co-operate in the investigation. The actual study thus comprises 155 probands (48 males and 107 females).

In all cases, the histological investigation was carried out by the same pathologist, Dr. *E. Christensen*, whose sound ability concerning tumour diagnosis was of the greatest significance in the definite grouping of the material.

The following groups of relatives of the selected probands were investigated:

- Parents
- Siblings
- Children
- Parents' siblings
- Half-siblings

Only relatives over the age of 10 years are included. In all, a total of approximately 5,700 relatives were investigated. As regards the parents' siblings, the authors have only included them if at least one of the sibling group was alive at the time of investigation. In this respect, the method employed differs from the usual *Weinberg* method. The authors obtained completely reliable information concerning all the individuals included in the analysis, but on the other hand, the absolute figures for the mortality,

particularly the mortality from cancer in the group of the parents' siblings, could scarcely be compared to the figures of the general population. As, however, the same technique was employed in the collection of the control material, comparison between the proband and control materials is permissible.

The Control Material comprises 2288 relatives of a total of 249 control individuals recruited from various social groups: manual workers, office personnel, nurses, old age pensioners and others. The relatives were investigated on exactly the same principles and with the same intensity as the proband material.

Both in the proband material and in the control material, one or more out of each of the larger groups of siblings in every family were questioned either personally or by means of a questionnaire.

Concerning each individual in the group of relatives involved, accurate information was thus obtained concerning:

Date and year of birth, place of birth.

Present or last known address.

If deceased, date of death.

Whether the individual concerned suffered from epilepsy, diabetes, intracranial tumour or cancer.

In the case of deceased relatives, the Death Certificates were always inspected, and in the case of hospitalized relatives the hospital records were reviewed in order to elucidate the diagnoses further if necessary.

In an attempt to decide whether the frequency of deaths from malignant growths or intracranial tumour increased in the relatives of the probands with intracranial tumour as compared to the general population, the control material was used as a basis of reference. The principles of the "life-table method" were adopted.

For each age group (10 year groups) the number of individuals who had gone through this group was estimated, viz., all those who had attained an age higher than the upper limit of the group + (approximately) half of those who were either in the group at the time of observation or who had died in the age group concerned. This forms an estimate of the number of individuals at risk in each age group. The intensity of the mortality in each age group may then be calculated as the ratio: number of deaths from cancer or intracranial tumour in the group concerned, number of individuals at risk in this group.

In estimating the expected number of deaths (from cancer or intracranial tumour) among the relatives of patients with intracranial tumours, each category of relatives was treated separately. The number of individuals at risk in each age group was calculated. This figure was multiplied by the ratio found in the same age group and category of relatives in the control material; a summation over all age groups then gives the total number of deaths expected in the category of relatives concerned. In this way a correction is made for the specific age distribution in each of the proband materials.

Results

The detailed findings in the authors' material appear from Tables 1-5 where for each group of relatives both the distribution of the relatives in various age groups at the time of observation and the incidence of intracranial tumour and cancer in the individual groups, are given. The object of such a detailed tabulation is to create the possibilities of comparing with other materials of a similar nature and to analyse these results with other methods.

The Occurrence of Intracranial Tumour Among Relatives

Among 1813 relatives of probands with *glioblastoma*, 5 cases of intracranial tumour were encountered.

Among 2020 relatives of probands with *astrocytoma*, 8 cases of intracranial tumour were encountered.

Among 282 relatives of probands with *medulloblastoma*, no case of intracranial tumour was found.

Among 1552 relatives of probands with *meningioma*, 2 cases of intracranial tumour were found.

Among 2288 relatives of the *control probands*, 10 cases of intracranial tumour were found.

Those probands among whose relatives secondary cases occurred, show no common characteristics either with regard to the specific histological nature of the tumour or its localization.

Information concerning the secondary cases is relatively heterogenous both with regard to the relatives of the probands and the control material.

The 5 secondary cases in the *group of glioblastomata* were diagnosed as follows:

Verified microscopically: one case (*astrocytoma*).

Autopsy finding without histological examination: one case.

Based more on clinical findings: 3 cases.

The 8 secondary cases in the *group of astrocytomata* were distributed as follows:

Verified histologically: one case (*oligodendroglioma*).

Operation or autopsy finding without microscopy: 4 cases.

Based merely on clinical signs: 3 cases.

The 2 secondary cases in the *group of meningiomata* were diagnosed as follows:

Verified microscopically: one case (*glioblastoma multiforme*).

Autopsy finding without microscopic examination: one case.

The 10 secondary cases in the *control material* were distributed as follows:

Histologically verified: 6 cases (3 *glioblastomata*, one *glioma* in cerebellum without signs of malignancy, 2 *oligodendrogliomata*).

Autopsy findings without histological examination: 2 cases.

Based merely on clinical signs: 2 cases.

Table 1

Age distribution and incidence of malignant neoplasm (c)
and intracranial tumour (tc) among relatives of probands with glioblastoma

Age Group	Fathers		Mothers		Brothers		Sisters		Sons		Daughters	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
10-19					1	6		9	21	2	17	
20-29		1			1	14	1	8	41	1	38	2
30-39		5		4	16	13	19	10	58	1	45	2
		(1c)		(1c)		(1tc)		(1c)				(1tc)
40-49		7		12	56	8	63	13	22		20	1
		(2c)		(4c, 1tc)		(1c)	(1c)	(8c)	(1c)			(1c)
50-59	2	24	2	21	99	19	99	15	2			
		(4c)		(8c)	(1c)	(6c)	(3c)	(5c, 1tc)				
60-69	4	33	5	25	56	11	68	13				
		(4c)		(4c)	(1c)	(2c)		(4c)				
70-79	15	48	21	47	20	5	31	7				
		(10c)	(2c)	(7c, 1tc)	(1c)		(1c)	(2c)				
80-	7	28	12	30	2		2	1				
	(2c)	(1c)		(3c)								
Total	28	146	40	139	251	76	283	76	144	4	120	5
(close relatives)	(2c)	(22c)	(2c)	(27c, 2tc)	(3c)	(9c, 1tc)	(5c)	(20c, 1tc)	(1c)			(1c, 1tc)
Age Group	Paternal uncles		Paternal aunts		Maternal uncles		Maternal aunts		Half brothers		Half sisters	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
10-19		4		4		2		7		1		
20-29		5		3		4		2				
30-39		2		4		2		4	3	1	1	
						(1c)		(2c)				
40-49		2	3	5		8	1	5	3		3	
		(1c)				(1c)		(2c)				
50-59	8	7	4	7	6	10	5	6	4	3	7	
		(2c)		(3c)		(1c)		(1c)				
60-69	14	16	20	12	14	9	18	10	1		5	
		(4c)		(2c)		(2c)		(5c)				
70-79	24	18	29	15	24	12	24	17	2		1	
		(3c)		(4c)		(3c)	(2c)	(4c)				
80-89	5	8	10	7	18	10	7	4	1			
				(1c)		(1c)		(1c)				
Total	51	62	66	57	62	57	55	55	14	5	17	0
(distant relatives)		(10c)		(10c)		(9c)	(2c)	(15c)				

Table 2

Age distribution and incidence of malignant neoplasm (c)
and intracranial tumour (tc) among relatives of probands with astrocytoma

Age Group	Fathers		Mothers		Brothers		Sisters		Sons		Daughters	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
10-19					19	3	13	3	30		33	
20-29	1	3	1	1	23	6	25	2	38	1	34	
						(1tc)						
30-39	5	3	9	3	65	7	52	8	18		22	
		(1tc)				(2tc)		(1c)				
40-49	16	9	13	7	73	8	91	5	5		9	
		(2c)		(1c, 1tc)		(1c)		(1tc)				
50-59	10	15	13	15	53	6	66	7			1	
		(7c)	(1c)	(3c)	(1c)	(1c)	(1c)	(2c, 1tc)				
60-69	12	23	25	26	35	7	38	3				
		(10c)	(1c)	(7c)	(1c)	(3c)						
70-79	17	26	21	23	5	2	5	3				
	(1c)	(4c)		(2c)								
80-	7	22	6	11	2							
		(1c)		(2c)								
Total	68	101	88	86	275	39	290	31	91	1	99	
		(1c)	(24c, 1tc)	(2c)	(15c, 1tc)	(2c)	(5c, 3tc)	(1c)	(3c, 2tc)			

Age Group	Paternal uncles		Paternal aunts		Maternal uncles		Maternal aunts		Half brothers		Half sisters	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
10-19					6	3		3	2		1	
20-29	3	5	6	15	2	4	2	6	1	1	2	
								(1tc)				
30-39	9	5	15	8	13	5	10	8	2		7	
		(1c)		(1c)								
40-49	19	6	24	3	25	9	28	6	10		6	
		(1c)		(1c)		(2c)						
50-59	28	10	31	5	36	14	39	11	2		3	
		(4c)	(1c)	(2c)		(1c)	(1c)	(1c)				
60-69	30	12	27	9	31	14	39	12	1	2	3	
		(1c)		(3c)	(1c)	(3c)		(5c)				
70-79	40	11	31	13	33	10	17	9				
	(1c)	(4c)	(1c)	(2c)		(1c)		(2c)				
80-	9	4	4	2	8	5	5	11				
						(1c)		(2c)				
Total	138	53	138	61	148	64	140	66	18	3	22	
	(1c)	(11c)	(2c)	(9c)	(1c)	(8c)	(1c)	(10c, 1tc)				

Table 3

Age distribution and incidence of malignant neoplasm (c)
and intracranial tumour (tc) among relatives of probands with meningioma

Age Group	Fathers		Mothers		Brothers		Sisters		Sons		Daughters	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
10-19					6	3	2	5	23			20
20-29		1			4	14	8	10	50	1		31
30-39	1	1	1	8	16	6	26	6	47	1		44
				(1c)		(1c)	(1c)			(1c)		
40-49	2	10	2	14	44	10	54	11	36	1		25
		(2c)		(1c)		(2c)		(2c)				
50-59		13	4	12	65	12	68	12	8			6
		(4c)		(6c)	(1c)	(3c)	(2c)	(6c)				
60-69	7	25	6	26	61	11	54	12				
		(6c)		(5c)		(3c)		(4c, 1tc)				
70-79	10	33	8	41	29	10	31	5				
		(9c)		(5c)	(1c)	(3c)	(1c)	(2c)				
80-	10	34	11	20	1	1	8	1				
		(3c)				(1c)						
Total	30	117	32	121	226	67	251	62	164	3		126
		(24c)		(18c)	(2c)	(13c)	(4c)	(14c, 1tc)		(1c)		

Age Group	Paternal uncles		Paternal aunts		Maternal uncles		Maternal aunts		Half brothers		Half sisters	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
10-19				2		1		1				
20-29		5	2		2	2	1	5				
30-39	2	2	1	5	3	1	2	1				1
		(1tc)		(1c)								
40-49	3	4	1	2		4	6	2	4			1
				(1c)		(2c)		(1c)				
50-59	5	7	1	5	3	7	5	6				
		(2c)		(1c)		(1c)		(2c)				
60-69	8	16	8	14	7	8	11	5	1		1	1
		(6c)		(4c)		(2c)		(2c)				(1c)
70-79	16	16	15	13	19	5	14	7	1	2		2
	(1c)	(7c)		(3c)		(1c)	(1c)	(1c)				
80-	7	8	13	1	7	6	7	7		1	1	
	(1c)											
Total	41	58	41	42	41	34	46	34	6	3	4	3
	(2c)	(15c, 1tc)		(10c)		(6c)	(1c)	(6c)				(1c)

Table 4

Age distribution and incidence of malignant neoplasm (c)
and intracranial tumour (tc) among relatives of probands with medulloblastoma

Age Group	Fathers		Mothers		Brothers		Sisters		Sons		Daughters	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
10-19					9	2	8					
20-29			1		8		7					
30-39	7		8		5	1	4					
40-49	8	1	7	2			2					
		(1c)										
50-59	3	1	6	1		1	2					
				(1c)		(1c)						
60-69	3		1		1	1	1					
70-79				1	1			1				
80-	1	1										
Total	22	3	23	4	24	4	24	1				
		(1c)		(1c)		(1c)						

Age Group	Paternal uncles		Paternal aunts		Maternal uncles		Maternal aunts		Half brothers		Half sisters	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
10-19		1		2	1		3		4		1	
20-29			1	2	7	1	6	1			3	
30-39	8	1	9	2	10	1	7					
40-49	13	1	11		10		14					
50-59	11	2	9	2	6	2	10					
		(1c)		(1c)								
60-69	2		3	1			4					
				(1c)								
70-79		1	1									
80-	2			1								
Total	36	6	34	10	34	4	44	1	4		4	
		(1c)		(2c)								

Table 5

Age distribution and incidence of malignant neoplasm (c) and intracranial tumour (tc) among relatives of control probands

Age Group	Fathers		Mothers		Brothers		Sisters		Sons		Daughters	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
10-19					3	11		16	21	6	15	5
								(1c)	(1tc)		(2tc)	
20-29		1		6	8	15	8	12	60	5	39	3
								(1c)				
30-39		11		17	22	15	15	7	74	3	56	7
				(1c)				(1tc)			(1c)	
40-49		16	4	12	45	23	36	18	35	2	50	2
		(3c)		(3c)	(3c, 1tc)			(4c)			(2c)	
50-59	9	38	6	15	64	35	74	23	3		21	2
		(6c)		(4c)	(9c, 3tc)	(1c)	(15c)				(1c)	
60-69	8	46	13	32	64	51	97	40	3			
		(12c)		(6c)	(1c)	(11c)		(10c)				
70-79	7	63	12	60	45	32	38	27				
		(10c)		(10c)		(7c)		(3c)				
80-	9	41	7	65	11	4	17	6				
		(5c)		(6c)				(1c)				
Total	33	216	42	207	262	186	285	149	196	16	181	19
		(36c)		(30c)	(1c)	(30c, 4tc)	(1c)	(33c, 1tc)	(2c)	(1tc)	(1c)	(3c, 2tc)
Age Group	Paternal uncles		Paternal aunts		Maternal uncles		Maternal aunts		Half brothers		Half sisters	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
10-19		3		1		3		3		1	1	
20-29		4		1		4		1	2	1	1	1
30-39		1	1	2	1	6		7	5			
40-49	2	4	5	4	8	13	3	5	3	3	3	
		(1c)				(3c)			(1c)			
50-59	11	5	12	7	9	9	9	7	7	2	6	2
				(2c)		(1c, 2tc)		(3c)			(1c)	(1c)
60-69	16	15	15	8	12	13	15	10	7	2	2	
		(3c)		(4c)		(2c)	(1c)	(2c)				
70-79	11	9	10	13	23	17	22	10	4		1	
				(4c)		(7c)		(3c)				
80-	10	5	6	9	9	12	10	11	1	1		
		(1c)		(3c)		(1c)		(2c)		(1c)		
Total	50	46	49	45	62	77	59	54	29	10	14	3
		(5c)		(13c)		(14c, 2tc)	(1c)	(10c)		(2c)	(1c)	(1c)

It appears without any further calculations that the number of cases of death from intracranial tumour among the relatives of patients with glioblastoma, meningioma, and medulloblastoma, respectively, does not exceed the number observed in the control material.

The number of secondary cases observed in the relatives of patients with astrocytoma may seem rather high. In order to obtain a basis for comparison, the number of secondary cases expected was calculated according to the method described above, using the intensity of mortality from intracranial tumours found in the control material. In this way the expected number of secondary cases among the near relatives of patients with astrocytoma was calculated as 4.3 and 8 were actually observed. This difference is not significant (as judged from the Poisson distribution).

Eight of the probands were *twins*. In all eight cases discordance existed as regards intracranial tumour. The pairs of twins are tabulated below (□ = unaffected male, ○ = unaffected female, ■ and ● = affected).

The zygosity diagnosis was elucidated as follows: Pairs no. 1 and 4: polysymptomatic similarity test including blood groups. Pairs no. 2, 7 and 8: Evidence from the family, including a number of photographs.

- | | | |
|----------------------------|----------------|---------------------------|
| 1) ■ ——— | □ | monozygotic, discordant |
| glioblastoma | 46 years | |
| died at 40 years | alive and well | |
| 2) ■ ——— | □ | dizygotic, discordant; |
| glioblastoma | died | co-twin died from chronic |
| died at 53 years | at 55 years | cor pulmonale |
| 3) ■ ——— | ○ | dizygotic, discordant |
| glioblastoma | 55 years | |
| died at 53 years | alive and well | |
| 4) ■ ——— | □ | monozygotic, discordant |
| fibrillar astrocytoma | 20 years | |
| operated upon at 15 years, | alive and well | |
| alive aged 20 years | | |
| 5) ■ ——— | ○ | dizygotic, discordant |
| protoplasmic astrocytoma, | 35 years | |
| died at 16 years | alive and well | |

- 6) ● ————— □ dizygotic, discordant
 astrocytoma, operated
 upon at 4 years,
 alive at 9 years 9 years
 alive and well
- 7) ■ ————— □ dizygotic, discordant
 meningioma, operated
 upon at 60 years,
 died at 61 years 74 years
 alive and well
- 8) ● ————— ○ dizygotic, discordant
 medulloblastoma, operated
 upon at 10 years,
 died at 10 years 20 years
 alive and well

□ = male, ○ = female

In 2 cases only (one proband with glioblastoma and one proband with astrocytoma) could consanguinity be demonstrated between the parents of the probands (first cousins). Thus no increased consanguinity exists in the material and no support is provided for the assumption of recessive hereditary factors.

It must thus be concluded that familial occurrence of gliomata and meningiomata seems to be a rare phenomenon. Secondary cases of intra-

Table 6

Comparison between the observed and expected number of cases of death from cancer among the near relatives of probands with intracranial tumour (including the age groups 10-80 only)

Probands with		Fathers	Mothers	Brothers	Sisters
Glioblastoma	observed number	21	24	9	20
	expected number	(24.0)	(17.7)	(13.9)	(19.8)
Astrocytoma	observed number	23	13	5	3
	expected number	(18.9)	(12.1)	(7.2)	(8.7)
Meningioma	observed number	21	18	12	14
	expected number	(21.8)	(13.6)	(15.7)	(17.3)

cranial tumours do not occur more frequently in this material in any of the groups of relatives than might be anticipated. Nor does the limited material of twins support the supposition that hereditary factors play a major part in the development of these forms of tumours.

The Genetic Relationship of Gliomata and Meningiomata to other Forms of Malignant Growth

In Table 6 the expected and observed number of cases of death from cancer is given for each group of near relatives in the 3 proband materials. The expected number is calculated as described above. It appears that nowhere do significant differences exist between the number expected and observed.

Table 7

Cases of malignant neoplasms among relatives of probands with intracranial tumour and relatives of controls. Type and site of tumour.

Type and site	Relatives of patients with			Relatives of controls
	glioblastoma	astrocytoma	meningioma	
Buccal cavity and pharynx	2	5	3	3
Digestive organs and peritoneum	58	46	63	87
Respiratory system	8	6	3	7
Breast	12	9	10	15
Male genital organs	3	1	3	2
Uterus	14	6	11	16
Other female genital organs	3	1	1	4
Urinary organs	5	7	6	8
Skin	1	1	0	0
Brain ¹	5	8	2	10
Thyroid	0	1	0	4
Unspecified sites (carcinoma)	14	10	8	24
Lymphatic system (sarcoma)	5	0	0	1
Lymphogranulomatosis, Hodgkin	1	0	3	1
Multiple myeloma	2	0	0	0
Leukemia	4	3	2	4
Sarcoma	6	0	4	8
All malignant neoplasms	143	105	119	194

Classification according to Manual Internat. Statistical Classification (Bull. W. H. O. Suppl. 1, 1948).

¹) all cases of intracranial tumour are included.

Further the risk of death from cancer for each sex and each group of relatives was individually calculated. The results are not reproduced here as they are only of limited general interest. No significant differences were found regarding the risk of death from cancer, either on mutual comparison with the groups of relatives in the 4 materials, or between each of them and the control material. It appeared from these calculations that the control material had been adequately investigated, as the risks for fathers and the male siblings of the parents were approximately equal as were also the risks for mothers and the female siblings of the parents.

Thus, the present materials do not show any increase in the frequency of deaths from cancer among the relatives of patients with intracranial tumours.

Table 7 shows the type and localization of the malignant tumours which were found among the relatives in the various proband materials and in the control material. It appears that sound agreement exists between the relative incidence of the various forms of malignant growths, but with one single exception. The group of mesodermal tumours shows a higher incidence in the group glioblastomata than in the other groups together. This difference is significant ($P \leq .04$), but it is probably a random observation.

The final conclusion to be drawn from these results is consequently that no definite relation exists between the various forms of intracranial tumour on the one hand, and malignant growths localized elsewhere on the other.

The Interrelation between Intracranial Tumours and Recklinghausen's Disease and Tuberous Sclerosis

The case records of the 535 probands in this series were reviewed in a search for signs of Recklinghausen's disease (R.d.) or tuberous sclerosis (t.s.).

As stated previously, histological examination of the brain (or the tumour only) was performed in all cases, and none of the specimens presented any definite changes suggesting a diagnosis of R.d. or t.s.

Two of the probands presented cutaneous signs resembling those found in R.d.:

1. A female, born in 1905, with a diagnosis of fibrillary astrocytoma, had a number of large, macular pigmentations and a few cutaneous, nodular fibromata scattered over the body. The patient presented no signs of epilepsy or mental retardation. Similar cutaneous signs were found in the father and one of the brothers of this patient, and the other brother had had one typical attack of epilepsy in his youth. This is undoubtedly a case of familial R.d.

2. A female, born in 1881, with a suprasellar meningioma, presented a number of sessile and pedunculate cutaneous fibromata. The family history was negative. None of her 7 siblings, her 4 children or her parents had any cutaneous signs or symptoms of epilepsy or mental deficiency.

A more detailed analysis of the occurrence of signs of R.d. or t.s. among the relatives of patients with intracranial tumours, is being undertaken. The detailed report will be published later, but as a preliminary result it can be stated that signs of R.d. and t.s. are only rarely met with in the families of patients with intracranial tumours.

The Significance of Hereditary Factors in the Occurrence of Epileptic Symptoms in Patients with Intracranial Tumours

In his monograph on epileptic symptoms in patients with cerebral tumours, Lund [1952] ventilated the possibility that epileptic symptoms might occur more readily in patients with cerebral tumours who are hereditarily predisposed to epilepsy. This supposition was, however, only based on the finding that among patients presenting epileptic symptoms, a definite predisposition (familial occurrence of unquestionable cases of epilepsy) was more common (7.7 per cent) than is supposed to be the case in the general population.

To illustrate this question more fully, systematic questioning concerning the occurrence of epilepsy in the families in this investigation was undertaken. The results are tabulated in Table 8. For each form of tumour, the probands were divided into 3 groups, viz,

- 1) patients with generalized seizures;
- 2) patients with definite epileptic manifestations but never generalized seizures;
- 3) patients who did not exhibit any definite epileptic manifestations.

For each group the total number of relatives over the age of 10 years is stated, no correction for age being undertaken. A number of families are, however, excluded from this Table because no reasonably reliable information was available whether the proband presented epileptic symptoms or not.

In the case of the relatives, the number of patients with absolute certain epilepsy is given as well as the number of patients with probable epilepsy but in whom it has not been possible to confirm the diagnosis either because the patient had died long before the investigation or had never been hospitalized for the condition. On account of the difficulty in

Table 8

Incidence of epilepsy among relatives of patients with intracranial tumour

Patients with generalized seizures:

	Number of patients	Number of relatives	Epilepsy, unquestionable cases	Epilepsy, doubtful cases
Glioblastoma	21	240	1	1
Astrocytoma	52	616	5	3
Medulloblastoma	0			
Meningioma	29	341	1	1
	102	1197	7 = 5.9 ⁰ / ₀₀	5 = 4.1 ⁰ / ₀₀

Patients with focal seizures:

	Number of patients	Number of relatives	Epilepsy, unquestionable cases	Epilepsy, doubtful cases
Glioblastoma	26	293	3	
Astrocytoma	41	530	2	
Medulloblastoma	3	40		
Meningioma	44	411	2	
	114	1274	7 = 5.5 ⁰ / ₀₀	0 = 0.0 ⁰ / ₀₀

Patients without seizures:

	Number of patients	Number of relatives	Epilepsy, unquestionable cases	Epilepsy, doubtful cases
Glioblastoma	121	1201	2	1
Astrocytoma	73	804	5	1
Medulloblastoma	24	245	1	2
Meningioma	78	753	2	
	296	3003	10 = 3.3 ⁰ / ₀₀	4 = 1.3 ⁰ / ₀₀

differentiating exactly between idiopathic epilepsy and symptomatic epilepsy, such a division was not undertaken, but both groups are classified under one heading.

It is apparent from the Table that the incidence of epilepsy is greatest for the relatives of the patients who themselves had generalized seizures,

less for the relatives of the patients who had solely focal attacks, and least for the relatives of patients who did not present any epileptic manifestations. None of the differences recorded is, however, significant.

The results of the present investigation thus show the same tendency as found by *Lund*, and the hypothesis that the manifestation of epileptic symptoms in patients with organic lesions of the brain may be hereditarily determined to a certain extent, is given some support. However, the numerical data found are not convincing.

Conclusions

Hereditary factors play scarcely any part in the etiology of gliomata, medulloblastomata and meningiomata, and similarly, these tumour forms do not seem to have any genetic relation to malignant growths localized elsewhere. Epileptic symptoms in patients with cerebral tumours may possibly be based on a hereditary predisposition to epilepsy.

Summary

Among 1813 relatives of 179 probands with glioblastomata, 5 cases of intracranial tumour were encountered. Among 2020 relatives of 174 probands with astrocytomata, 8 cases of intracranial tumour were encountered. Among 282 relatives of patients with medulloblastomata, no case of intracranial tumour was found. Among 1552 relatives of 155 probands with meningiomata, 2 cases of intracranial tumour were found. Among 2288 relatives of 249 control individuals, 10 cases of intracranial tumours were encountered.

The frequency of deaths from cancer in the relatives of patients with intracranial tumours did not differ significantly from the frequency found among relatives of the control probands.

The incidence of epilepsy was found to be somewhat greater (5.9 ‰) among relatives of patients with generalized epileptic seizures than among relatives of patients who had no epileptic manifestations at all (3.3 ‰). However, this difference is not significant.

Zusammenfassung

Unter 1813 Angehörigen von 179 Probanden mit Glioblastom fanden sich 5 Fälle von intrakraniellern Tumor. Unter 2020 Verwandten von 174

Probanden mit Astrocytom wurden 8 Fälle mit intrakraniellern Tumor festgestellt. Kein Fall von intrakraniellern Tumor wurde unter 282 Angehörigen von Patienten mit Medulloblastom aufgefunden. Unter 1552 Verwandten von 155 Meningeom-Patienten entdeckte man 2 Fälle mit intrakraniellern Tumor. Von 2288 Angehörigen von 249 Kontrollfällen waren 10 an intrakraniellern Tumor erkrankt.

Verwandte von Patienten mit intrakraniellern Tumor starben nicht gesichert häufiger an Krebs als Verwandte von Kontrollfällen.

Epilepsie kam bei Verwandten solcher Kranken, die an generalisierten epileptischen Anfällen litten, etwas häufiger (5.9^0_{00}) vor als bei Angehörigen von Patienten, die überhaupt keine epileptischen Symptome hatten (3.3^0_{00}). Der Unterschied ist jedoch nicht statistisch gesichert.

Résumé

Parmi 1813 personnes apparentées à 179 probants, atteints de glioblastome, 5 cas de tumeur intracrânienne ont été rencontrés. Parmi 2020 individus apparentés à 174 probants avec astrocytome, on a trouvé 8 cas de tumeur intracrânienne. Par contre, parmi 282 individus appartenant aux familles des malades atteints de médulloblastome, aucun cas de tumeur intracrânienne n'a été relevé. Parmi 1552 personnes apparentées aux 155 probants avec méningiomes, 2 cas de tumeur intracrânienne ont été découverts. Parmi 2288 individus appartenant aux familles de 249 individus témoins, 10 cas de tumeur intracrânienne ont été trouvés.

La fréquence de mortalité due au cancer chez les personnes apparentées aux malades atteints de tumeur intracrânienne ne diffère pas significativement de la fréquence trouvée dans les familles des probants témoins.

La fréquence de l'épilepsie a été trouvée un peu plus haute (5.9^0_{00}) dans les familles dans lesquelles le probant est atteint de crise épileptique généralisée, que dans les familles de malades sans manifestation épileptique (3.3^0_{00}). Toutefois, cette différence n'est pas significative.

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A SCOTCH TAPE ALUMINIUM POWDER TECHNIQUE FOR RECORDING DERMAL PATTERNS

By JAN MOHR

Genetic studies of dermal patterns have been considerably hampered by technical difficulties. It seems important therefore to report in detail any substantial improvement in technique.

The technique described here gives excellent prints of fingers, palms, toes and soles even of the smallest and most restless children; the individual sweat pores and other minutia are well recorded. It takes little time and has been found suitable for routine studies, for instance of families who have been examined in their homes. Lastly, it is not objectionable to the persons being examined, since there is no danger of spoiling clothes or furniture, as may happen with the ink methods.

The method is a modification of the technique described by *Böök* [1948] and *Cotterman* [1951], who both recorded prints on Scotch tape. *Böök* dusted the skin with talcum powder, chalk or graphite, while *Cotterman* found it preferable to paint the skin with Indian ink. In our hands the latter method was not very effective, although we used the same kind of Scotch tape as *Cotterman*. Probably we did not obtain the right kind of Indian ink, although all the brands on sale in Oslo were tried. In any case this method is too time-consuming for routine studies, as indicated by *Cotterman* himself. The method described below is closer to that of *Böök*.

Materials and equipment

1. Scotch Acetate Film Tape no. 800. transparent. pressure sensitive adhesive tape, Minnesota Manufacturing Co., Saint Paul 6, Minnesota. Rolls of two widths, 2 and 6 inches, are sufficient. The latter width has to be ordered specially.
2. A bottle of 2.5% glycerol in 96% alcohol.
3. A jar of cotton pads.
4. A "dusting box" of aluminium powder. The bottom of this box is removed and replaced by a double or triple layer of gauze, through which the powder is shaken out. The aluminium powder is such as is ordinarily used by the police, and is mixed with 92% lycopodium.
5. Flakes of celluloid.
6. A photographer's roller.
7. Labels, pencils etc.

Procedure

The subject is first asked to wash his hands and feet with soap and water. When dry, he is seated on a chair with his feet on a towel placed on the floor. The fingers, palms, toes and soles are then washed with pads of cotton soaked with liberal amounts of glycerol-alcohol. When the alcohol has evaporated, it will be found that a suitable amount of glycerol has been deposited on the skin; this makes the technique applicable to dry skin. The fingers and hands are then dusted with aluminium powder. Any excess powder must be thoroughly removed by blowing or wiping with a dry pad of cotton.

When taking the print the examiner sits on a chair in front of the subject. The subject places his hand on the knee of the examiner with the

palm upwards and the fingers a little apart. A 6 inch flake of Scotch tape, which has previously been cut off to a suitable length from the roll, is now applied to the hand starting from the finger tips and proceeding towards the wrist. Care must be taken to get the tape firmly fixed at the moment it touches the skin, so as to avoid double prints. After some experience it is usually possible to get fine prints of all the fingers and the whole palm on this single sheet. In the case of large hands, it is often necessary to make a separate print of the thumb, which may conveniently be done on a corner of the same sheet.

The patterns of the feet are recorded in a similar manner. The subject places his heel on the knee of the examiner; the skin is dusted with aluminium powder and excess powder removed. One end of a 6 inch Scotch tape of suitable length is placed just below the heel, and then contact is successively made with the whole sole by moving towards the toes. Just before the toes are reached, the tape is folded against the lateral side of the foot to make sure of recording the pattern on the lateral edge.

Before proceeding further the tape is released from the lateral edge. The toes have to be kept upwards so as to make accessible the important areas of the sole close to the toes. The tape is then applied to these areas, to the toes, and to the lateral areas of the sole close to the toes.

Although good prints of individual toes are often obtained by this procedure, we have found it necessary in practice to make separate prints of each toe. For this purpose pieces of the 2 inch tape are used.

Immediately after the prints have been taken, they are mounted permanently on celluloid. A flake of celluloid has in advance been placed on a table, carefully stretched, so as to get an entirely flat surface. The prints are mounted at one end first, the rest of the print being held vertically. The print is then rolled on by means of a photographer's roller, care being taken to get complete contact.

Besides celluloid, cellophane, and glass have been tried for mounting. But celluloid has proved preferable to both. The difficulty with cellophane is that it is almost impossible to get it sufficiently flattened out before the tape is rolled on, therefore disturbing air spaces are left between the cellophane and the rolled on tape. Glass is liable to break, and it is bulky and heavy, without offering any substantial advantage.

Examination of the prints

The prints are best examined on a table with a black surface and with strong oblique illumination from above. Sometimes details appear more

distinctly when the print is examined against a strongly illuminated white background.

Projection

The prints are very suitable for projection. The record to be projected is simply mounted between the two pieces of glass in a lantern slide.

Summary

A technique for recording dermal patterns which seems to have several advantages over previous procedures is described.

Zusammenfassung

Es wird eine Methode für die Gewinnung von Abdrücken der Hautleistenmuster beschrieben, die einige Vorteile gegenüber bisher angewandten Techniken zu bieten scheint.

Résumé

L'auteur décrit une nouvelle technique pour prendre les empreintes digitales qui semble avoir plusieurs avantages sur les méthodes connues.

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A NOTE ON HOGBEN'S "FIGURATE SERIES AND FACTORIAL NOTATION". A GENERALIZATION

By R. V. PARKER, Norfolk

Let: -

$$x^{[n]r} = x(x+r)(x+2r)\dots(x+\overline{n-1}r). \quad \dots\dots(i)$$

Then: -

$$(a+b)^{[n]r} = \sum_{t=0}^n n(t) \cdot a^{[n-t]r} \cdot b^{[t]r} \quad \dots\dots(ii)$$

where a and b and r are any rational quantities, b and r positive or negative, and n a positive integer.

We have the following special cases: -

$$(a+b)^n = \sum_{t=0}^n n(t) \cdot a^{n-t} \cdot b^t. \quad \dots\dots(iii)$$

which is Newton's Binomial Theorem, and is derived from (ii) when $r = 0$.

$$(a+b)^{(n)} = \sum_{t=0}^n n(t) \cdot a^{(n-t)} \cdot b^{(t)}. \quad \dots\dots(iv)$$

which is Vandermonde's Theorem for factorial powers, and is derived from (ii) when r is -1 .

$$(a+b)^{[n]} = \sum_{t=0}^n n(t) \cdot a^{[n-t]} \cdot b^{[t]}. \quad \dots\dots(v)$$

which is a formula forming part of a generalization of Vandermonde's Theorem given by Professor Hogben, in "Acta Genetica et Statistica Medica", 5, 1955, pp. 115-133, and is derived from (ii) when $r = 1$.

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LIBRI

Paul Maslow: Intuition Versus Intellect: The Life Science Press, Valley Stream. New York, 1957. X + 277 pp. \$ 4.50.

It is not unusual that an author with psychoanalytical orientation employs words such as "constitution" or "genetic", most frequently in inverted commas. There is, however, seldom an opportunity such as this for further elucidation of the conceptions such expressions may be understood to cover.

The author of this book employs the word "genetic" to a great extent, partly in promising headings such as "The genetic neurosis", "Samples of genetic neurosis", "The genetic basis of sexual psychologies" and partly in various constellations such as "genetic memories" or "the genetic compound of psychological memories". The latter conceptions are identical with "collective unconscious" or "psychological inheritance", propounded by *C. Jung* and the book acts as a support of Jung's "analytical psychology". In 46 chapters a series of philosophical subjects such as faith, doubt, intuitive morality, ethical principles etc. are treated and, more particularly, the problem of intuition versus intellect. Employing tones suggestive of the Day of Judgement, the author advocates that the time is now ripe to let intuition play a leading rôle in the evolution of mankind. "Unless intuitive loving kindness permeates all aspects of behaviour and thought during the nuclear age, the future holds sudden death for great masses of people and possibly the annihilation of all organic life on this planet", is the sinister final message of the book.

Judging from the list of references, the author's knowledge of genetics is limited to a single work by *Galton* and a book by *A. Scheinfeld*. In the few instances where the book shows a fairly direct relation to human genetics, the author's abysmal ignorance of what is commonly understood by genetics is revealed. This is apparent from isolated quotations from his dejectingly naive contemplations: "Apparently psychopathy represents the complete failure to utilize the moral inheritance which provides the basis of conscience. This failure can either be caused by a genetic defect at birth (such as the absence of a moral gene) or a process within the contemporary organism which results in forgetting, partial or complete, of the ancestral experiences from which moral intuitions are derived. Can there be something at work, a biochemical action for example, which makes genetic memories (not only moral) stronger or weaker, quite distinct from the normal cumulative growth of ancestral experience?" The author, in a philosophic analysis of embryological conditions finds "direct evidence of the inheritance of acquired characteristics" (only in the case of man, however, and not for the remainder of the animal kingdom). This, however, seems no more surprising than the author's complaint that geneticists refuse to accept such theories.

The reviewer considers it doubtful whether this book will appeal to many readers in the medical world, even to disciples of *Jung*. It is entirely void of interest for geneticists.

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Der Bluterstamm von Tenna und seine Nachkommen 1650-1955

Haemophilia B
in the Wide-Spread Kindred of Tenna Haemophiliacs

Von

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Die Umgebung von Tenna

1 : 200 000 — Reproduziert mit Bewilligung der Eidg. Landestopographie vom 16. Oktober 1956.

EINLEITUNG

Die vorliegende Arbeit wurde anlässlich der sero-anthropologischen und genetischen Bestandesaufnahmen in den Walser Isolaten Graubündens (HUSER, 1953a, MOOR-JANKOWSKI, 1953) 1952 begonnen und parallel zu diesen weitergeführt, wobei sich die für die beiden Untersuchungsgebiete notwendigen genealogischen Nachforschungen gegenseitig vervollständigten.

Unsere Untersuchungen an den Blutern von Tenna hatten als Zielsetzung *nicht nur das Erfassen sämtlicher Bluter, sondern auch das Aufstellen einer weitgehend vollständigen Nachfahrentafel ihres ersten bekannten Stammelternpaares*. Diese liegt nun mit 3072 Personen in 13 Generationen aus der Zeit von etwa 1650 bis 1955 vor.

Das vorhandene Material gibt somit neben dem vollständigen Bild des haemophilen Erbganges der Tenner Bluter auch ein Bild der anverwandten, unter den gleichen Bedingungen lebenden, jedoch von der Haemophilie frei gebliebenen Nachkommenstämme. Es sollen dadurch genauere Vergleichsuntersuchungen über die genetischen Probleme der Haemophilie ermöglicht werden, wobei die hier durchgeführten nur einen Teil der Auswertungsmöglichkeiten des gebotenen Materials darstellen.

Die meisten Nachkommen des Stammelternpaares der Bluter von Tenna sind auch heute in Tenna und in den umliegenden Tälern ansässig (siehe Karte, S. 1). Bei der Materialaufnahme ist den Autoren die Kenntnis der Gegend und der Bevölkerung zugute gekommen: G. TRUOG ist seit 1934 in Versam als Talschaftsarzt für Tenna, das Safiental und Versam tätig; H. J. HUSER und J. K. MOOR-JANKOWSKI arbeiten seit mehreren Jahren an den sero-anthropologischen und genetischen Problemen der dortigen Isolate.

Die Aufnahme des Materials wurde vollständig anhand der Originalquellen durchgeführt. Die Angaben entstammen den Kirchenbüchern, den Registern der Zivilstandsämter und der Einwohnerkontrollen, den Krankengeschichten der Spitäler und der behandelnden Ärzte sowie den persönlichen Aussagen der untersuchten Probanden. Von den insgesamt 3072 erfaßten Personen mußten wir nur in 4 Fällen auf die Aufnahme von Personalangaben aus der Originalquelle verzichten und sie aus der Literatur (HOESSLY-HAERLE, 1930) übernehmen, da der betreffende Teil des Kirchenbuches aus dem Dorfarchiv verloren gegangen ist. Im übrigen wurden uns die für die Arbeit HOESSLY-HAERLE (1930) vorhandenen Unterlagen nicht zur Verfügung gestellt und solche für die früheren Arbeiten

über die Bluter von Tenna sind nicht mehr auffindbar gewesen. Es gelang uns jedoch nach Aufstellen der Nachfahrentafel anhand der Originalquellen, die Angaben aller früheren Veröffentlichungen zwanglos zu identifizieren. Dieses Vorgehen gestattete uns in mehreren Fällen, die Aussagen der früheren Autoren wesentlich zu korrigieren bzw. zu vervollständigen.

Die Bluter und ihre Familien, insbesondere auch die *sicheren und die möglichen Konduktorinnen*, wurden einer differentialdiagnostischen Laboruntersuchung auf *Haemophilie A und B* unterzogen. Sie erfaßte mit den 68 untersuchten Probanden fast alle für die haemophile Vererbung in Frage kommenden Nachkommen des Tenner Bluterstammes sowie einige Kontrollpersonen und gestattete somit einen Überblick über die gerinnungsphysiologische Erscheinungsform der Krankheit innerhalb einer sehr weit verzweigten Sippe gleicher Abstammung. Die Untersuchungen, durchgeführt von Dr. M. GEIGER, Gerinnungsphysiologisches Labor des Kantonsspitals Zürich (Prof. F. KOLLER), erfolgte im Rahmen der Untersuchung aller Bluter in der Schweiz, die vom Schweizerischen Nationalfonds zur Förderung der wissenschaftlichen Forschung finanziert wurde.

Die in der Schweiz ansässigen 11 Bluter und ihre Familien wurden während unserer Untersuchungen ebenfalls auf Farbensehen und CN-Geruchsempfinden geprüft.

Im *allgemeinen Teil* dieser Arbeit wird unsere Bestandesaufnahme beschrieben und das gebrachte Material ausgewertet.

Der *spezielle Teil* enthält die Beschreibung aller Fälle, die für die haemophile Vererbung von Interesse sind oder Anlaß zur Diskussion gegeben haben.

Die *Nachfahrentafel* im Anhang zerfällt in 3 Teile, die den 3 Hauptstämmen unter den Nachkommen des ersten Stammelternpaares der Bluter von Tenna entsprechen. Sie erfaßt 13 Generationen und enthält die gesamten bekannten Nachkommen des Stammelternpaares. Alle aufgeführten Personen sind mit einer Standortnummer versehen. Diese gestattet das Auffinden aller diskutierten Fälle im speziellen Teil dieser Arbeit und aller Personalangaben im Namenverzeichnis.

Das *Namenverzeichnis* enthält die genauen Personalangaben aller in der Arbeit erfaßten Personen, die nach ihren Standortnummern aus der Nachfahrentafel geordnet sind. Es wird nicht veröffentlicht, wurde jedoch einigen schweizerischen und ausländischen Instituten überreicht (siehe S. 76) und kann unter Wahrung des ärztlichen Geheimnisses eingesehen werden.

Bei der Bearbeitung des Bluterstammes von Tenna waren wir stets bemüht, nicht nur die Resultate unserer Auswertung zu bringen, sondern auch *den ganzen Verlauf der Arbeiten und das gesamte Material in einer Form darzustellen, welche die Überprüfung unserer Aussagen und Berechnungen jederzeit möglich macht.* Zu diesem Zweck wurde vorerst unsere Bestandesaufnahme beschrieben und alle Auswertungsarbeiten genau geschildert. Das Material wurde nach allen im Text besprochenen Gesichtspunkten gegliedert und wo nötig mit eigens vervollständigten Auszügen aus der Nachfahrentafel illustriert. Sämtliche uns bekannten Fehlerquellen wurden diskutiert. Bei strittigen Problemen wurden alle Argumente und Gegenargumente angeführt und mit Originalangaben belegt, die stets im Text oder im Namenverzeichnis mit Quellenbezeichnungen versehen und somit überprüfbar sind.

Um jedoch das Benützen unserer Angaben für weitere Vergleiche und Berechnungen auch ohne Zuziehen des Namenverzeichnisses zu ermöglichen, wurden zusätzliche Tafeln und tabellarische Zusammenstellungen in die Arbeit eingereiht.

Auch die bisherige Literatur über die Bluter von Tenna mußte eingehend besprochen werden, um die früheren Mißdeutungen und Fehler auf Grund von neuen Erkenntnissen und vollständigeren Angaben zu korrigieren.

Um dem Leser seine eigene objektive Urteilsbildung zu ermöglichen, haben wir somit den allgemeinen Teil der Arbeit mit zahlreichen zusätzlichen Angaben belasten müssen, was die Darstellung schwerfälliger und komplizierter gestaltet hat. Wir hoffen jedoch, daß bei eingehendem Studium, für welches ja die Arbeit bestimmt ist, der Nachteil der Schwerfälligkeit durch die Vorteile der genauen Darstellungen aufgewogen wird.

Sollten uns in den zahlreichen Tafeln und Aufstellungen einige Fehler unterlaufen und trotz der wiederholten Kontrollen unbemerkt geblieben sein, was wir in Anbetracht des Ausmaßes und der Kompliziertheit des Zahlenmaterials als möglich erachten, so werden sie immer von dem aufmerksamen Leser anhand der Nachfahrentafel und des Namenverzeichnisses korrigiert werden können.

Wir danken den untersuchten haemophilen Patienten und den Familien, die uns bereitwillig Auskunft erteilt haben, wie auch den Herren Dr. E. BONIFAZI, Dr. P. STEINER und Dr. J. VERAGUT in Thusis, Dr. J. BUNDI und Dr. B. CATHOMAS in Ilanz und Dr. H. MARX in Malans für die Angaben über die behandelten Bluterpatienten, die gewährte Einsichtnahme in die entsprechenden Krankengeschichten und die Hilfe bei unseren Untersuchungen.

Fräulein Maria SCHNEEBERGER, Mitautorin des Namenverzeichnisses, hat als wissenschaftliche Assistentin bei der Zusammenstellung des Materials von Anfang an aktiv mitgearbeitet. Wir verdanken ihr auch die Lösung von vielen technischen Problemen, die sie beim Aufzeichnen der Nachfahrentafel und der übrigen graphischen Darstellungen mit viel Geschick und Geduld gemeistert hat.

Unser besonderer Dank gebührt Prof. S. ROSIN, der uns seit 1954 in entgegenkommender Weise mit zahlreichen Anregungen und Ratschlägen für die Bestandesaufnahme, die Auswertungsarbeiten und bei der redaktionellen Darstellung zur Seite gestanden und die statistische Bearbeitung unseres Materials übernommen hat. Herrn Dr. W. H. RUOFF danken wir für seine wertvolle Beratung bei unseren genealogischen Nachforschungen und bei der graphischen Darstellung der Ergebnisse. Wir danken ferner Prof. F. KOLLER und Dr. M. GEIGER für die uns zur Verfügung gestellten unveröffentlichten Resultate der Untersuchungen auf Haemophilie A und B, welche Dr. M. GEIGER an unserem Krankengut durchgeführt hat.

Manche Vorschläge und Anregungen haben wir unseren englischen Freunden, den Herren Dr. A. E. MOURANT, Dr. P. M. SHEPPARD und Dr. C. A. B. SMITH zu verdanken. Auch Herrn Prof. L. S. PENROSE sind wir für seine wertvollen Ratschläge zur Auswertung unseres Materials verpflichtet. In Anbetracht des von den englischen Forschern gezeigten Interesses, haben wir unsere graphischen Darstellungen zweisprachig beschriftet und der Arbeit eine englische Zusammenfassung beigelegt, um auch den der deutschen Sprache unkundigen Lesern die Ergebnisse unserer Nachforschungen zugänglich zu machen.

Zu Dank verpflichtet sind wir sodann den Herren Prof. A. FRANCESCHETTI, Privatdozent Dr. D. KLEIN und Prof. F. E. LEHMANN für ihr reges Interesse, den Rat und die Unterstützung, welche an dem Zustandekommen und Gelingen unserer Arbeit in ihrer jetzigen Form maßgebend beteiligt sind.

Die Einsichtnahme in die Archive der Gemeinden, der Kreise, der Landschaften und der Korporationen wie auch in die Kirchenbücher und die Zivilstandsregister wurde uns durch die Bewilligung des Staatsarchivs Graubünden ermöglicht, wofür wir Herrn Staatsarchivar Dr. R. JENNY unseren Dank aussprechen.

Der Schweizerische Nationalfonds für Förderung der wissenschaftlichen Forschung hat die Redaktion der vorliegenden Arbeit wie auch die Arbeiten an dem Namenverzeichnis in den Jahren 1955 und 1956 finanziell unterstützt.

Die Redaktion der *Acta Genetica et Statistica Medica* und der Verlag S. Karger haben in verdankenswürdiger Weise die verlagstechnisch nicht einfache Veröffentlichung unserer Ergebnisse übernommen.

I. Allgemeiner Teil¹⁾

1. Historische, demographische und geographische Angaben über den Abstammungsort und das Verbreitungsgebiet des Bluterstammes von Tenna und seiner Nachkommen

Der Bluterstamm von Tenna wird nach dem Dorfe benannt, in welchem das erste bekannte Stammelternpaar Albrecht WALTHER (Standortnummer in der Nachfahrentafel: Generation II. Laufnummer 2) und Ursula BUCHLI (II. 3), wie auch 18 ihrer Bluternachkommen in der Zeit von 1676 bis 1862 gelebt haben.

Das Bündner Bergdorf Tenna, 1645 m ü.M., liegt auf einem nach Südosten geneigten Hang des Safientales. Die Einwohner sind durchwegs Walser, also jene deutschsprechenden Kolonisten, die im 13. und 14. Jahrh. aus dem Wallis nach Graubünden gekommen sind und sich hier zum Teil bis in die Gegenwart in relativer Isolierung erhalten haben.

Tenna selbst wurde als eine Walserkolonie im 14. Jahrh. gegründet. Um die gleiche Zeit wurden auch die Talsohle des Safientales und einige Hof-siedelungen des am Eingang des Tales gelegenen romanischen Dorfes Versam von den Walsern besiedelt (Joos, 1946). In überlegener Zahl eingewandert, haben sie sich wahrscheinlich rasch mit den spärlichen autochthonen Romanen vermischt oder sie auch zum Teil verdrängt, da das Tal bereits seit dem 14. Jahrh. als walserisches Gebiet galt.

Die Walserbevölkerung von Tenna, Safien und Versam kann heute als homogen und das ganze Gebiet als ein relatives Isolat angesehen werden, und zwar u.a. auf Grund von genealogischen (MOOR-JANKOWSKI, HUSER und ROSIN, in Vorbereitung) und sero-anthropologischen (IKIN, MOURANT KOPEĆ, MOOR-JANKOWSKI und HUSER, 1957) Untersuchungen. Diese Situation ist auf die historische Entwicklung (Joos, 1946) und die geographisch abgeschlossene Lage zurückzuführen.

¹⁾ Für Abkürzungen und Zeichenerklärung siehe Kapitel 7, Darstellung der Ergebnisse.

Die Endogamie der Bevölkerung ist zum Teil schon aus der Nachfahrentafel der vorliegenden Arbeit ersichtlich. Noch heute leben die Nachkommen des ersten Stammelternpaares der Bluter von Tenna mehrheitlich (siehe Tab. 1) in Tenna und Umgebung, welches Gebiet auf der Karte S. 1 abgebildet ist.

Tab. 1. Geographische Verteilung der heute lebenden Nachkommen des Bluterstammes von Tenna, eingeteilt nach Generationen und Teilen der Nachfahrentafel¹⁾ (siehe Bemerkung (1), (2) und (3) zu Tab. 1, S. 7)

Geographical Distribution of Descendants of Tenna Hemophiliacs Alive in 1956 grouped by generations and parts of Table of Descendants¹⁾ (see notes (1), (2) and (3) to Tab. 1, p. 7)

Teile der Nachfahrentafel	Generation	Tenna und Umgebung ²⁾	Kanton Graubünden	übrige Schweiz	Ausland	unbekannter Wohnort	
Parts of Table of Descendants	Generation	Tenna and environs ²⁾	Grisons	The rest of Switzerland	Foreign countries	Domicile not recorded	
A	IX.	23	2	—	11	4	
	X.	81	14	18	2	10	
	XI.	91	15	21	—	20	
	XII.	20	—	3	—	6	
	XIII.	—	—	—	—	1	
B	IX.	45	4	1	6	37	
	X.	178	28	16	5	97	
	XI.	233	53	40	10	65	
	XII.	52	30	18	2	38	
	XIII.	—	—	—	—	14	
C	IX.	5	2	1	4	7	
	X.	55	16	9	5	26	
	XI.	95	24	30	2	23	
	XII.	59	—	10	—	4	
	XIII.	—	—	—	—	—	
total	IX.	73	8	2	21	48	
	X.	314	58	43	12	133	
	XI.	419	92	91	12	108	
	XII.	131	30	31	2	48	
	XIII.	—	—	—	—	15	
Gesamttotal IX.–XIII.		937	188	167	47	352	1691

¹⁾ 3 Teile der Nachfahrentafel im Anhang.

3 parts of Table of Descendants in the Appendix.

²⁾ Das ganze Gebiet wie auf Karte S. 1 abgebildet.

The whole area as given by the map on p. 1.

Verteilung im Ausland
Distribution in Foreign Countries

Generation	Frank- reich	Italien	Öster- reich	England	in Ruß- land verschollen	USA	Chile	Neu- seeland	un- bekannt	
IX.	2	—	4	—	—	5	4	4	2	
X.	—	—	5	—	—	5	2	—	—	
XI.	—	1	—	4	1	6	—	—	—	
XII.	—	—	—	—	—	2	—	—	—	
XIII.	—	—	—	—	—	—	—	—	—	
total	2	1	9	4	1	18	6	4	2	47

Die vor 1870 geborenen nicht weiterverfolgbaren und nicht weiterverfolgten Personen (siehe Tab. 4) sind nicht mitberechnet.

Persons born before 1870 who were either untraceable or not followed up (see Tab. 4) are not included.

- (1) Die Personen mit den uns unbekannten Wohnorten aus der Tab. 1 sind ähnlich wie die vollständig erfaßten Personen in Tenna und Umgebung, bzw. in Graubünden und in der übrigen Schweiz verteilt, nur wenige davon leben im Auslande.
Genauere Angaben über ihre Wohnorte sind uns unbekannt, weil wir ihre Personalangaben den Bürgerregistern ihrer Heimatgemeinden (siehe S. 22 ff.) entnommen haben. Dort werden aber nur die Daten und die Orte der Geburten, der Eheschließungen und der Todesfälle, jedoch keine Wohnorte aufgezeichnet. Die Geburten, die Trauungen und die Todesfälle erfolgen aber meistens in der nahen Umgebung des Wohnortes und geben somit seine ungefähre Lage an.
Wenn es uns folglich auch nicht möglich ist, diese Wohnorte genau anzugeben, so konnten wir immerhin feststellen, daß die geographische Verteilung dieser Fälle derjenigen der übrigen vollständig erfaßten Personen entspricht.
 - (2) Um eventuelle weitere Berechnungen, Vergleiche und Zusammenstellungen anhand unseres Materials zu erleichtern, ist die Tab. 1 wie auch weitere Tabellen, nach den Teilen der Nachfahrentafel A, B und C eingeteilt.
 - (3) Um mehrfaches Auszählen der wiederholt auftretenden Personen, die in den 3 Teilen der Nachfahrentafel jeweils mit Verweisen versehen sind, zu vermeiden, ist folgendermaßen vorgegangen worden:
 - Vorkommen von Verweisen in der gleichen Generation: Beide Ehepartner wurden zu dem Teil der Nachfahrentafel gezählt, in welcher ihre Kinder eingezeichnet sind.
 - Vorkommen von Verweisen in zwei verschiedenen Generationen: Beide Ehepartner wurden zu dem Teil der Nachfahrentafel und zu der Generation gezählt, in der sie in bezug auf die Generationenfolge das erste Mal vorkommen.
- NB. Bei dieser Auszählung kommt es vor, daß die Generation der Eltern gegenüber der Generation der Kinder in der Generationenfolge verschoben wird.

Auf Grund der historischen Angaben und der Nachforschungen in den seit der zweiten Hälfte des 17. Jahrh. erhaltenen Kirchenbüchern ergibt sich, daß die Bevölkerungsbewegung in Tenna und im Safiental in den letzten Jahrhunderten fast ausschließlich im Sinne der Abwanderung erfolgte. Ortsfremde siedelten sich in den beiden Gemeinden nur ausnahmsweise und fast ausschließlich durch die seltene Einheirat an, was schon an sich einer Einwanderung sehr enge Grenzen setzte. Die natürliche Vermehrung führte zu Übervölkerung, bei gleichzeitigem Auftreten einer Ertragsverminderung des Weidelandes infolge der Klimaverschlechterung in den Alpen um 1600 (WINKLER, 1955a, 1955b).

Alle diese Gründe wirkten nicht nur gegen eine fremde Einwanderung, sondern ergaben auch die ständige Abwanderung der Bevölkerung (siehe auch JENAL, 1947), wie sie für die letzten 150 Jahre mit Zahlen in der Tab. 2 belegt wird.

Tab. 2. Bevölkerungsbewegung im Safiental und in Tenna
Migrations in Safien Valley and in Tenna

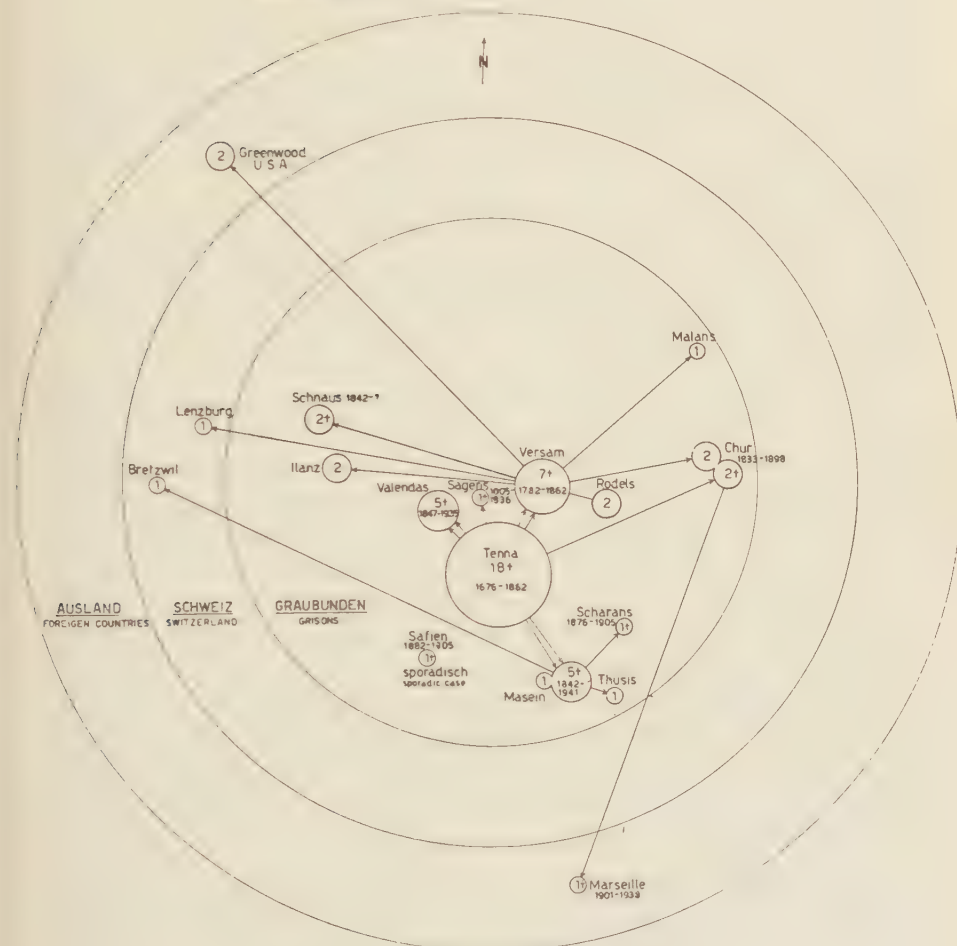
Zähljahre Years of registration	Quellenangabe Sources	Einwohnerzahl - Inhabitants		
		Safiental Valley of Safien	Tenna	Safiental + Tenna Valley of Safien + Tenna
1806	JENAL, S. 189 (1947)	770	157	927
1850	JENAL, S. 189 (1947)	685	162	847
1860	JENAL, S. 189 (1947)	606	148	754
1870	JENAL, S. 189 (1947)	599	146	745
1880	JENAL, S. 189 (1947)	546	142	688
1888	JENAL, S. 189 (1947)	526	153	679
1900	JENAL, S. 189 (1947)	455	130	585
1910	JENAL, S. 189 (1947)	441	138	579
1920	JENAL, S. 189 (1947)	428	129	557
1930	JENAL, S. 189 (1947)	412	135	547
1941	JENAL, S. 189 (1947)	445	126	571
1950	Eidgenössisches Stati- stisches Amt (1951)	453	141	594

Die aus der Tab. 2 ersichtliche geringere Bevölkerungsabnahme in Tenna als im Safiental läßt sich durch bessere landwirtschaftliche Nutzungsmöglichkeit des sonnseitig gelegenen Tenna erklären. Immerhin war auch hier die Abwanderung größer als der ständige Geburtenüberschuß. Sie erfolgte größtenteils in die umliegenden Täler, wie aus Tab. 1 und der Karte S. 1 ersichtlich.

Eine ähnliche Bevölkerungsbewegung kann auch in den Walser Hofsiedlungen von Versam festgestellt werden; ein zahlenmäßiges Erfassen war hier jedoch nicht möglich, da abgesehen von den Walser Hofsiedlungen das Dorf teilweise von Romanen bewohnt ist und die Ergebnisse der Volkszählung jeweils die gesamte Dorfbevölkerung erfaßten.

Fig.1
GEOGRAPHISCHE VERTEILUNG DER TENNER BLUTER 1956

Bei verstorbenen Blutern (mit † versehen) ist der Geburtsort massgebend, bei den Lebenden der Wohnort
Jeder Pfeil entspricht einem abgewanderten Träger des haemophilen Gens



GEOGRAPHICAL DISTRIBUTION OF TENNA HEMOPHILIACS

Hemophiliacs deceased before 1956 (marked †) are listed at their places of birth, those alive in 1956 at their domiciles

Each arrow corresponds to an emigrated carrier of the gene of hemophilia

Die Tatsache, daß seit der Geburt des letzten Bluters in Tenna im Jahre 1828 dort kein neuer Bluterfall mehr aufgetreten ist, läßt sich durch die Abwanderung der haemophilen Genträger erklären, welche im Rahmen der Abwanderungsbewegung der übrigen Bevölkerung lag.

Die Migrationsverhältnisse sowie die geographische Verteilung der Geburtsorte der verstorbenen Tenner Bluter und die Wohnorte der gegenwärtig lebenden (siehe Fig. 1) entsprechen im allgemeinen den Verhältnissen bei der gesamten Tenner Bevölkerung.

2. Literatur über die Bluter von Tenna

Die Bluter von Tenna gelten in der Literatur als der größte bekannte Bluterstamm und sind bereits in einigen Monographien bearbeitet worden. In mehreren Werken wurden sie auch als Beispiel zugezogen und ausführlich diskutiert.

Da sich unsere Arbeit vorwiegend auf eigene Nachforschungen und Untersuchungen stützt, beschränken wir uns in unserer Literaturbesprechung lediglich auf Originalbeschreibungen und erwähnen nur zusätzlich einige bekannte Kompilationsarbeiten, in welchen die Tenner Bluter ausführlich besprochen wurden.

Die chronologisch erste Beschreibung stammt von Dr. med. Friedrich THORMANN (1837 und 1840). Er praktizierte 1827 bis 1853, anfänglich in der Gruob (Ilanz und Umgebung), später in Chur, wobei Tenna stets in seinem Wirkungskreis lag. Es kann angenommen werden, daß er seinen Arztberuf mit Erfolg ausgeübt hat, da er 1843 zum Suppleanten und 1852 zum ordentlichen Mitglied des Bündner Sanitätsrates gewählt wurde.¹⁾

THORMANN beschreibt seine Behandlung eines Bluters im Jahre 1829 und erwähnt, daß noch andere Glieder der Familie an einer «idiosyncrasia haemorrhagica» leiden, die sich von Großvätern über gesunde Töchter auf Enkel vererbt. Trotzdem das von THORMANN angegebene Alter und das Todesjahr des Patienten um einige Jahre korrigiert werden mußten, kann dieser mit Sicherheit als CVII.199 (siehe speziellen Teil dieser Arbeit) identifiziert werden. Der Autor gibt keine genaueren Angaben über die anderen Bluterfälle aus der Familie.

¹⁾ Angaben aus: 1. Jahresbericht des Sanitätsrates pro 1827, Manuskript im Staatsarchiv Graubünden.
2. Zusammensetzung des Sanitätsrates, 1807 ff., Manuskript im Staatsarchiv Graubünden.
3. Schweiz. Zeitschrift für Medizin, Chirurgie und Geburtshilfe, 1853, S. 430.

Von den beiden Veröffentlichungen von THORMANN steht uns die 1837 erschienene zur Verfügung; sie soll nach BULLOCH und FILDES (1912) mit der 1840 veröffentlichten identisch sein.

Die ersten ausgedehnten Nachforschungen bei den Blutern von Tenna wurden von Dr. med. Peter Josef Alois VIELI durchgeführt. Er lebte 1815 bis 1858 in Rhäzüns und wirkte auch in Tenna. Die Zeitdauer seiner Praxisausübung konnte in den vorhandenen Archivquellen nicht festgestellt werden; ihr Beginn kann bei Berücksichtigung der damals üblichen Ausbildungsdauer um 1840 angesetzt werden. Auch VIELI scheint nach den überlieferten Angaben¹⁾ ein erfolgreicher Arzt gewesen zu sein. Er war Mitglied verschiedener Kommissionen im kantonalen Sanitätswesen und seine Mitgliedschaft in der Französischen Medizinischen Gesellschaft spricht für sein wissenschaftliches Interesse.

Die erste Veröffentlichung (1846) über seine Behandlung des Tenner Bluters BVI.106 (siehe speziellen Teil der Arbeit) im Jahre 1844 wurde vom Redaktor der veröffentlichenden Zeitschrift anhand der Berichte von VIELI verfaßt. Entweder waren jedoch die von VIELI übermittelten Angaben ungenau, oder aber ist sein Bericht unrichtig verstanden worden; auf jeden Fall enthält die Publikation einige Ungenauigkeiten und Unklarheiten. So werden zwar die Haemophilen als Bluter oder blutende Männer «*Bluters ou hommes saignants*» benannt (beide Bezeichnungen im Text als termini technici mit Kursiv hervorgehoben), jedoch spricht der Verfasser auch von «*femme Bluter*», worunter VIELI sicherlich keine weiblichen Haemophilen gemeint haben konnte, da er in seinen aus der gleichen Zeit stammenden Berichten an GRANDIDIER (1855a) das Vorkommen von weiblichen Blutern in Tenna ausdrücklich bestreitet. Aus der so entstandenen Verwirrung der Begriffe ergibt sich in der Veröffentlichung eine unklare Beschreibung des Vererbungsmodus, wenn er auch im gleichen Sinne wie der von THORMANN (1837) beschriebene verstanden werden kann. Im übrigen ist auch das Alter des Patienten unrichtig angegeben und dazu wird ein zweiter siebenjähriger Patient mit nichterblicher Blutungsneigung beschrieben, der dann in späteren Berichten von VIELI an GRANDIDIER (1877) als eingewanderter Fremder ohne verwandtschaftliche Verbindung zu Tenna bezeichnet wird. Bei diesem zweiten Patienten lag wohl in der Veröffentlichung vom Jahre 1846 eine Verwechslung oder ein Mißverständnis vor, ansonst hätte VIELI ihn sicherlich in seinen später veröffentlichten Mitteilungen an GRANDIDIER (1855a und 1877) ausführlich beschrieben, wie er dies sonst bei allen von ihm in Tenna untersuchten Fällen getan hat.

¹⁾ Nach Hist.-Biographischem Lexikon der Schweiz, 1934, Bd. VII, S. 244.

Eine wirkliche Bedeutung für die Kasuistik der Bluterfälle von Tenna hat aber erst die chronologisch zweite Veröffentlichung von VIELI, die anhand seiner Mitteilungen in der Monographie von GRANDIDIER (1. Aufl. 1855a, 2. Aufl. 1877) erschienen ist. Den «Bluterfamilien zu Tenna im Kanton Graubünden» wird dort ein separates Kapitel in Form von einer vollständigen kleinen Monographie gewidmet. Zuerst werden geographische und demographische Angaben über Tenna vermittelt. Die Zahl der Bluter wird im Jahre 1846 mit 16 und im Jahre 1854 mit 20 angegeben, worunter offensichtlich auch die nichthaemophilen Glieder der Bluterfamilien mitberechnet werden (vgl. Fig. 3 und Tab. 13). Es folgt eine längere allgemeine Beschreibung der haemophilen Symptome bei den Blutern in Tenna mit einigen Betrachtungen über ihre Konstitution und über die Vererbung der Krankheit nur durch Frauen, die «nach dortigem Ausdrucke als Conductoren gelten», wobei hervorgehoben wird, daß keine Fälle von Blutungen bei Frauen bekannt sind und ebenfalls «Man kennt 4 bis 5 Generationen hindurch kein Beispiel, daß Männer die Haemophilie fortgepflanzt haben». Anschließend wird von VIELI die Abstammung der Bluter besprochen, bis um 1770 zurückverfolgt und in 2 Stämme aufgeteilt, die er von 2 Stammelternpaaren abstammen läßt: Martin WEIBEL (B IV. 21) und Margreth WALTHER (B IV. 22), resp. Christian BÜHLER (C V. 74) und Anna BREHM (C V. 75), wobei die letzte von ihm unrichtigerweise Wilhelmine benannt wird. Bei der Aufstellung der Stammbäume stützt er sich auf eigene Untersuchungen der Bluterfamilien wie auch auf die Aussagen der Bevölkerung über die verstorbenen Bluter und ihre verwandtschaftlichen Beziehungen. Auch der Tenner Pfarrer war ihm beim Aufstellen der Stammbäume behilflich und behauptete, wohl um sich Arbeit zu ersparen, daß die Kirchenbücher «in großer Unordnung und erst von 1828 an benutzbar waren». Durch diese offensichtliche Irreführung – denn die Kirchenbücher sind bis um 1660 zurück gut erhalten und auch weitgehend ordentlich geführt worden – gelang es VIELI nicht, weiter als 3 bis 4 Generationen zurückzuverfolgen. Es litt darunter ebenfalls die Genauigkeit seiner aus mündlicher Überlieferung übernommenen Daten und Namen, wenn auch ein Teil der ungenauen oder unrichtigen Angaben zweifelsohne auf falsche Auslegung seiner auf französisch verfaßten Originalberichte an GRANDIDIER, oder auch auf Druckfehler zurückzuführen ist. So z. B. im Falle des Martin GARTMANN (B VI. 106), der in der Veröffentlichung von VIELI (1846) mit richtigem Namen, bei GRANDIDIER (1877) aber als GÄRTNER aufgeführt ist. Der gleiche Bluter ist, wie bereits BULLOCH und FILDES (1912) bemerkt haben, bei VIELI (1846) als der wohlhabendste Mann im Dorfe «le plus aisé du village», dagegen bei GRAN-

DIDIER (1855a) in der 1. Auflage als «der älteste Mann in Tenna» bezeichnet, wobei GRANDIDIER offensichtlich in VIELI's Mitteilungen «aisé» für «ainé» genommen hat. In der 2. Auflage (1877) wurde diese Mißdeutung mit Nachdruck berichtigt, wenn auch der falsche Name «GÄRTNER» belassen wurde. Es scheint also, daß VIELI die 1. Auflage der Monographie von GRANDIDIER gesehen hat und einige Berichtigungen noch anregen konnte.

Die 1. Auflage steht uns nur in anderswo veröffentlichten Auszügen zur Verfügung (GRANDIDIER, 1855b; HOESSLI, 1885; BULLOCH und FILDES, 1912). Wir beziehen uns daher meist auf die 2. Auflage (1877), die nach BULLOCH und FILDES (1912) keine zusätzlichen Angaben enthält, jedoch wie wir es gezeigt haben, von VIELI wohl gelesen und auch zum Teil korrigiert worden ist.

Anschließend an die genealogischen Angaben bringt VIELI (bei GRANDIDIER, 1877) ausführliche Beschreibungen der von ihm behandelten und der ihm bekannten Bluterfälle von Tenna, die im speziellen Teil unserer Arbeit jeweils kurz zusammengefaßt wiedergegeben sind. Als Letztes beschreibt VIELI (bei GRANDIDIER, 1877) einige Bluterfälle in Graubünden, außerhalb Tenna, die er zum Teil mit den Tenner Blutern in Verbindung bringt, was aber durch spätere Nachforschungen (siehe S. 56 ff.) nicht bestätigt werden konnte.

Trotz einiger Ungenauigkeiten sind die klinischen Beobachtungen und die haemophile Vererbung von VIELI richtig erfaßt und beschrieben worden; seine Tenner Stammbäume waren die größten der damaligen Literatur über Haemophilie und gaben auch den Anstoß zu späteren Bearbeitungen des Tenner Bluterstammes.¹⁾

GRANDIDIER veröffentlichte noch 1855 und 1863 Angaben aus den Mitteilungen von VIELI in «Schmidt's Jahrbücher» (1855b, 1863). Er bringt dort jedoch keine zusätzlichen Angaben, da es sich im wesentlichen um Auszüge aus seiner Monographie (1855a) handelt.

Die nächste Originalbeschreibung des Tenner Bluterstammes wurde von Dr. med. Anton HOESSLI (1885) als Dissertationsarbeit an der Basler Universität veröffentlicht. Sie ist, wie aus ihrer Einleitung ersichtlich, in den Jahren 1877–1878 entstanden. HOESSLI praktizierte in dieser Zeit in

¹⁾ Es ist reizvoll zu beobachten, daß die Bevölkerung des abgelegenen Bergdorfes Tenna nicht nur den haemophilen Vererbungsmodus richtig beobachtet hat, sondern auch die Bezeichnung «Bluter» fast gleichzeitig – wenn nicht früher – mit seiner Einführung durch NASSE (1820) benützt und für die Genträgerin den Ausdruck «Konduktor» geprägt hat, welcher dann durch die Beschreibung der Tenner Bluter von GRANDIDIER (1855a) in die Literatur eingeführt wurde.

Thusis, wobei Tenna in seinem Einzugsgebiet lag. Er selbst konnte keinen Bluter untersuchen, sammelte jedoch sorgfältig Angaben von anderen in der Gegend praktizierenden Ärzten und von der Bevölkerung und untersuchte auch einige nichthaemophile Mitglieder der Bluterfamilien. Es ist sein Verdienst, in den Kirchenbüchern von Tenna und Versam nachgeforscht zu haben, trotz der von VIELI überlieferten Berichte über deren Unbenutzbarkeit. Dort fand er als erster die Vermerke über den Verblutungstod von B III. 7, C IV. 24, C IV. 25 und C IV. 30, die in der Zeit von 1676 bis 1741 gelebt haben und bis heute als die ersten bekannten Bluter von Tenna gelten. In weiteren 7 Bluterfällen (vgl. Tab. 13) aus dem 19. Jahrh. konnte er dank den Sterberegistervermerken die Beschreibungen von THORMANN (1837) und von VIELI (1846. und bei GRANDIDIER, 1855a und 1877) bestätigen bzw. ergänzen. Mit Hilfe der Kirchenbücher gelang es ihm auch, zahlreiche weitere Angaben der früheren Autoren richtigzustellen und zu vervollständigen. Er stellte eine weitgehend komplette Genealogie der Bluter von Tenna auf und nahm an, «daß alle Bluter von Tenna einen gemeinsamen Ursprung haben». Immerhin behielt er die von VIELI eingeführte Einteilung in 2 Bluterstämme bei, wenn auch jeweils um 2 Generationen weiter zurückverfolgt. Als Stammelternpaare werden von ihm Albrecht WALTHER (II. 2) copuliert mit Ursula BÜCHLI (II. 3) – bei HOESSLI irrtümlicherweise als Ursula BÜHLER bezeichnet; siehe auch HOESSLY-HAERLE (1930) S. 339 – und Hans GARTMANN (III. 9) copuliert mit Ursula WALTHER (III. 10) angegeben. Er diskutiert zwar die naheliegende Vermutung, daß die letzterwähnte III. 10 Tochter des ersterwähnten Ehepaares II. 2 und II. 3 gewesen ist, lehnt sie aber infolge einer unrichtigen Auslegung der Angaben in den Kirchenbüchern ab (Diskussion siehe im speziellen Teil dieser Arbeit bei III. 10).

Über die Erbllichkeit des Leidens sagt HOESSLI: «Die Vererbung der Haemophilie geschieht nicht selten vom Vater durch die Tochter auf die Enkel (männlich); ebenso häufig ist die Vererbung von der Mutter durch die Tochter auf die Enkel (männlich) und am seltensten vom Vater direkt auf den Sohn», wobei er in dem letzten Fall die Vererbung von Albrecht WALTHER (II. 2), den er in seinem Stammbaum als Konduktor bezeichnet, auf den Bluter Samuel WALTHER (III. 7) annimmt. Er ist sich bewußt: «Eine solche Auffassung... scheint... mit dem, was man bisher als Gesetz für die Verbreitung und Vererbung des Leidens ansprach, in argem Widerspruch zu stehen» und versucht sie dadurch zu erklären, «daß die Vererbungsfähigkeit beim männlichen Geschlecht viel stärker ist, als man gemeinlich angenommen hat, und scheint uns darum, auch die Übertragung der Krankheit vom Vater auf den Sohn... keine Unmöglichkeit zu

sein.» Dieser letzte Vererbungsmodus wird übrigens von HOESSLI nur eingeführt, weil ihm das Vorkommen eines männlichen (II.2) und eines weiblichen (III.10) WALTHER – die ja in Wirklichkeit Vater und Tochter sind –, unter seinen beiden Stammelternpaaren auffällt. Er sieht aber darin nur den Beweis, daß die Haemophilie durch die Familie WALTHER, gleich ob weiblich oder männlich, in Tenna vererbt und verbreitet wurde.

Im übrigen ist jedoch die Arbeit HOESSLIS sehr klar geschrieben und gibt ein gutes Bild des Tenner Bluterstammes bis 1880; es kann auch heute an den damaligen Beschreibungen nur wenig geändert werden. Die Angaben sind mit viel Fleiß und Sorgfalt gesammelt, und es ist meist nur Sicheres aufgenommen worden. Der Autor meidet bewußt unklare Berichte und Vorstellungen, so z.B. über haemophile Blutungen bei Frauen, deren Vorkommen in Tenna er durchwegs ablehnt und die diesbezüglichen «Nachrichten für lückenhaft» hält, ähnlich wie bei den «vielen Fragen, die sich an die etwas dunkeln und unsichern Begriffe der latenten und rudimentären Haemophilie knüpfen».

1912 erschien die große kompilatorische Arbeit von William BULLOCH und Paul FILDES, in der alle bis damals veröffentlichten Haemophiliefälle, jeweils mit Stammbäumen versehen, beschrieben wurden. In ihrer Beschreibung der Bluter von Tenna stützen sich die Autoren auf die Angaben von THORMANN (1837 und 1840), VIELI (1846; bei GRANDIDIER, 1855a und 1877) und, vor allem, auf die Monographie von HOESSLI (1885). Trotzdem es sich bei der Veröffentlichung von BULLOCH und FILDES um keine Originalbeschreibung handelt, wollen wir hier kurz auf sie eingehen, da sie bis heute ein sehr wertvolles Standardwerk über einen großen Teil der bekannten Haemophiliefälle geblieben ist und eine große Verbreitung gefunden hat. Die dort zusammengetragenen Bluterfälle von Tenna sind genau und klar beschrieben und graphisch in Form von Stammbäumen zusammengestellt. Doch mußten die Mißdeutungen und Fehler der früheren Autoren in die Bearbeitung zwangsweise mit übernommen werden, da BULLOCH und FILDES jede Kontrollmöglichkeit fehlte. Dennoch gelang es ihnen, einige dieser Fehler als solche zu bezeichnen (z.B. der Fall Martin GARTMANN, B VI.106, bei GRANDIDIER, und der Fall Hans BÜHLER, CV.80, den HOESSLI wohl infolge eines Druckfehlers mit unrichtigem Sterbe- und Todesjahr angegeben hat), was die Genauigkeit ihrer Bearbeitung beweist. Nur bei Samuel WALTHER, III.7, unterläuft den Autoren ein Irrtum, da sie ihn, wahrscheinlich infolge eines Übersetzungsfehlers, mit dem damals in Tenna amtierenden Pfarrer aus Splügen verwechseln. Es ergibt

sich daraus eine Mißdeutung, demzufolge sie seinen Wohnort als unbekannt und ihn selbst als in Splügen begraben bezeichnen.

BULLOCH und FILDES nehmen die Haemophilievererbung nur durch Bluterschwestern an. Aus diesem Grunde behaupten sie, daß die Ehefrauen der Bluter Samuel WALTHER (III.7) und Peter B. (B VI. 51), wie auch die Frau des mutmaßlichen Bluters Christian BÜHLER (CV.74), unbekannterweise Konduktorinnen gewesen sind. Sie versuchen dadurch die erfolgte Vererbung der Haemophilie auf die Enkel dieser beiden Bluter zu erklären, eine Stellungnahme, die im Lichte der heutigen Erkenntnisse dahinfällt. Im übrigen lassen die Autoren die Einteilung in 2 Bluterstämme nach HOESSLI unverändert bestehen. Sie bereichern die Kasuistik der Tenner Bluterfälle durch die Beschreibung des C VIII.323 durch CANTANI (1872), auf die im speziellen Teil dieser Arbeit näher eingegangen wird, sind aber nicht in der Lage, ihn in die Stammbäume einzureihen.

1930 erschien die bis jetzt ausführlichste Arbeit über die Tenner Bluter von Dr. med. Gertrud Tabitha HOESSLY-HAERLE aus der Medizinischen Universitäts-Poliklinik Zürich. Die Autorin, Schwiegertochter des verdienstvollen Verfassers der beispielhaften ersten kompletten Monographie über die Bluter von Tenna, A. HOESSLI (1885), nahm sich die Mühe, die früheren Angaben anhand der Kirchenbücher und der Aussagen der noch lebenden Zeugen zu überprüfen und bis 1930 zu vervollständigen. Sie verbrachte mehrere Monate in Tenna und Umgebung, konsultierte die Kirchenbücher von Tenna, Versam und Safien und besuchte die Bluter und ihre Familien. Sie versuchte auch die Blutgerinnungsbestimmungen nach BÜRKER durchzuführen, was ihr aber durch die ablehnende Haltung der Probanden verunmöglicht wurde; in 26 Fällen führte sie Blutgruppenbestimmungen durch¹⁾. Die so entstandene Arbeit enthält einen Stammbaum mit annähernd 1000 Personen, Beschreibungen von mehreren Blutern und deren Verwandten aus dem Tenner Stamm, Übersicht der Fachliteratur und längere Abhandlungen über Genese und Therapie der Haemophilie. Von Interesse sind hier der Stammbaum sowie die Beschreibung des Tenner Bluterstammes, und wenn wir auch vielerorts mit HOESSLY-HAERLE nicht

¹⁾ Die Ergebnisse dieser Untersuchungen von HOESSLY-HAERLE sind auf dem Stammbaum in ihrer Arbeit verzeichnet. Sie fand bei 14 Probanden die Blutgruppe A, bei 3 die Blutgruppe B, bei 9 die Blutgruppe AB und in keinem Fall die Blutgruppe 0. In Anbetracht der Tatsache, daß wir bei der dortigen Walserbevölkerung die in Europa höchsten Häufigkeiten der Blutgruppe 0 und sehr niedrige Häufigkeiten der Blutgruppen B und AB feststellten (MOOR-JANKOWSKI, 1954), kann die Richtigkeit der Ergebnisse von

einiggehen können, so möchten wir hier das Ausmaß der von ihr geleisteten Forschungsarbeit und die Bedeutung der von ihr aufgenommenen Angaben, die sonst verlorengegangen wären, gebührend anerkennen. Auch bleibt ihr das Verdienst, den Stammvater des ersten Bluterstammes von HOESSLI (1885), Albrecht WALTHER (II.2), als Vater der Stammutter des zweiten Bluterstammes von HOESSLI (1885), Ursula WALTHER (III. 10), identifiziert zu haben. HOESSLI selbst hat diese Möglichkeit zwar auch diskutiert, sich jedoch zu ihrer Annahme nicht entschließen können, wie dies im speziellen Teil dieser Arbeit bei III.10 ausführlich besprochen wird.

HOESSLY-HAERLE ist von allen Autoren die erste gewesen, für den Tenner Bluterstamm das Vorkommen von «weiblichen Partialblutern» und von «rudimentären Blutern» anzunehmen, eine Stellungnahme, die wir als völlig unbegründet betrachten und *durchwegs ablehnen müssen*. Das Problem wird von uns in besonderen Kapiteln eingehend besprochen.

Bei der Suche nach einer genetischen Erklärung der von ihr eingeführten «Partialbluterinnen» und «rudimentären Bluter» entwickelt die Autorin seitenweise eigene Vererbungsformeln, die weder mit den Tatsachen, die schon den Autoren des 19. Jahrh. bekannt waren, noch mit den Erkenntnissen der Genetik in Einklang zu bringen sind. Auszüge davon werden von uns bei Besprechung dieser «Partialbluterinnen» und der «rudimentären Bluter» von HOESSLY-HAERLE, wie auch im speziellen Teil dieser Arbeit wiedergegeben.

Wenn wir uns mit den Schlußfolgerungen, die HOESSLY-HAERLE aus dem von ihr gesammelten Material gezogen hat, oft nicht einverstanden erklären können, so stellt dieses Quellenmaterial an sich einen wertvollen Beitrag zur Beschreibung des Tenner Bluterstammes in der Zeit 1885–1930 dar. Im Laufe unserer Nachforschungen anhand der Originalquellen wie Kirchenbücher, Krankengeschichten, Familienaufzeichnungen und Zeugen-

HOESSLY-HAERLE bezweifelt werden. In einigen Fällen konnten Untersuchungen neueren Datums zur Kontrolle zugezogen werden:

Proband	Untersuchung von Hoebly-Haerle	Kontrolluntersuchung
C X. 612	A	0 Dr. WEIDMANN, 1940, Blutspendedienst SRK
C XI. 666	B	0 Dr. WEIDMANN, 1940, Blutspendedienst SRK
C. XI. 667	A	0 Kantonsspital Chur, 1953
C. XI. 668	A	0 Dienstbüchlein der Armee
B. X. 319	A	A Dr. WEIDMANN, 1940, Blutspendedienst SRK
C. XI. 669	A	A Dienstbüchlein der Armee

aussagen, konnten wir feststellen, daß HOESSLY-HAERLE mit großer Wahrscheinlichkeit alle in ihrer Berichtszeit lebenden Bluter aus dem Tenner Stamm erfaßt hat. In einigen Fällen konnte sie damals auch weiterzurückreichende Angaben von inzwischen verstorbenen Angehörigen der Bluterfamilien erhalten, wodurch interessante Zusammenhänge innerhalb des Tenner Stammes aufgeklärt werden konnten, wie z.B. die endgültige Einreihung des von CANTANI (1872) beschriebenen Bluters C VIII. 323 in den Tenner Stammbaum.

In diesem Zusammenhang möchten wir die weitgehende Zuverlässigkeit der Beobachtungen und Augenzeugenberichte, die allen Autoren von der Bevölkerung in Tenna und Umgebung mitgeteilt wurden, hervorheben. Die Vertrauenswürdigkeit dieser Aussagen hängt mit dem Interesse der Einwohner der Bündner Dörfer, vor allem aber der abgelegenen Isolate wie Tenna, an der Lokal- und Familientradition und an allen Begebenheiten des Dorflebens zusammen, die erstaunlich lange in Erinnerung behalten werden.

Während unserer Bestandesaufnahme für die vorliegende Arbeit, wie auch bei unseren sero-anthropologischen Untersuchungen (MOOR-JANKOWSKI, 1954; HUSER, MOOR-JANKOWSKI und ROSIN, 1956) in zahlreichen Dörfern der gleichen Gegend, haben wir in jeder Siedlung eine oder mehrere Personen getroffen, welche die meisten Lebensdaten ihrer Mitbewohner und sogar deren Eltern und Großeltern kannten, und zwar meist auf den Tag genau. Was hier aber über die Verhältnisse im 20. Jahrh. gesagt wird, gilt noch im verstärkten Maße für die Untersuchungen der Autoren aus dem 19. Jahrh. Die damalige sehr starke Abgeschlossenheit der Tenner Gegend von der Aussenwelt und das Fehlen der modernen Zerstreuungsmöglichkeiten mußte die Pflege der kleinen Ortsgeschichte und der Lokaltradition noch ganz besonders fördern. Für die Bevölkerung war aber, wie wir es auch später zeigen werden, alles, was die Bluterkrankheit anbetraf, von ganz besonderem Interesse. Dadurch kann den Berichten, die von den Autoren oft über weit zurückliegende Begebenheiten aufgenommen wurden und die sich nicht selten gegenseitig bestätigen, eine mehr als übliche Glaubwürdigkeit beigemessen werden.

Gleichzeitig mit der Monographie von HOESSLY-HAERLE (1930) wurden die Tenner Bluter im grundlegenden Werk «Die Haemophilie» von Prof. Dr. med. H. SCHLOESSMANN (1930) kurz beschrieben. Die Unterlagen dazu wurden SCHLOESSMANN von Prof. Dr. med. E. HANHART, Zürich, geliefert, der die Angaben von HOESSLY (1885) zum Teil bis 1928 vervollständigte. Da die veröffentlichten Stammtafeln unvollständig sind und zum Teil auch Unstimmigkeiten aufweisen, die jedoch in einigen Fällen offensichtlich auf Druckfehlern beruhen, haben wir Prof. HANHART um Erklärung dieser Unzulänglichkeiten gebeten und führen hier die erhaltene Antwort an:

«Ich wünsche nur insofern zitiert zu werden, als die Angaben von Schloebmann, die er auf Grund eines Briefes von mir machte, korrigiert werden müssen. Aus Rücksicht auf Frau Dr. Hoeßly habe ich meine seinerzeitigen Untersuchungen in bezug auf diese Bluter-Gruppe nicht publiziert; sie sind nun auch längst überholt.»

SCHLOESSMANN behauptet übrigens (S.41), daß «der sehr ausgedehnte von Vieli und Hoeßli erforschte Stamm der Bluter in Tenna von Gelenkerscheinungen frei ist». Schon VIELI (bei GRANDIDIER, 1877, S.61) schreibt jedoch über C VIII. 299: «hat heftige Schmerzen, meist im Hüftgelenke, seltener in den Knien». Auf diesen Fall kommt auch SCHLOESSMANN in einer Randbemerkung S. 234 zu sprechen, bezeichnet ihn jedoch als «sehr fraglich». Wir können mit SCHLOESSMANN hier nicht einiggehen, schon in Anbetracht mehrerer Fälle von Gelenkerscheinungen bei Tenner Blutern, die in den späteren Generationen von HOESSLY-HAERLE (1930), PIANTA (1953) und von uns beobachtet wurden. Bei dem familiären Krankheits-typus der Haemophilie, der auch von SCHLOESSMANN (1930) an seinem Material beobachtet wurde, können wir hier aus den Erscheinungsformen bei den heute lebenden Tenner Blutern auf die früheren Generationen Rückschlüsse ziehen und auch bei diesen das Vorkommen der Gelenk-erscheinungen annehmen.

1953 wurden die letzten Generationen der haemophilen Stammbäume in Graubünden von Dr. med. Marc Antonio PIANTA beschrieben. Die Arbeit erschien als medizinische Dissertation an der Universität in Bern, aus dem Laboratorium von Prof. Dr. med. A. FONIO in Bern. Der Autor, selbst ein Bündner, bereiste Graubünden und die übrige Schweiz, um in den Bluterfamilien, bei den behandelnden Ärzten und in den Spitälern nach den in den letzten Generationen aufgetretenen Bluterfällen zu for-schen. Für den Bluterstamm von Tenna konnte er 3 neue Haemophilie-fälle beschreiben. Es gelang ihm auch, 7 von HOESSLY-HAERLE (1930) be-reits beschriebene Kranke weiterzuverfolgen, darunter 2 vor seiner Be-standesaufnahme verstorbene (vgl. Tab. 13). PIANTA erklärt in seiner Ein-leitung, daß es ihm nicht möglich gewesen sei, die sehr zahlreichen zur Zeit seiner Untersuchung lebenden Nachkommen des Tenner Bluterstammes vollständig zu erfassen. So bringt er auch keine Angaben über die weiteren 2 seit der Untersuchung von HOESSLY-HAERLE (1930) verstorbenen und 4 inzwischen neu aufgetretenen Haemophiliefälle (vgl. Tab. 13).

Von den insgesamt 10 beschriebenen Blutern wird in 8 Fällen eine kurze Anamnese und der Status aus der Zeit der Untersuchung angegeben, von den 2 Verstorbenen werden katamnestische Angaben übermittelt. Gerin-nungszeitbestimmungen wurden vom Autor bei keinem der untersuchten Bluter, wohl aber bei ihren Müttern durchgeführt. Für die Bluter selbst beschränkt sich der Autor nur auf 3 Fälle, wo er die Gerinnungszeitbe-stimmungen – und in 1 Falle Prothrombinzeit – aus den früheren Spital-krankengeschichten übernimmt, ohne aber die Methoden dieser Bestim-mungen zu nennen, wodurch ihre Bewertung verunmöglicht wird. Bei den

Konduktorinnen führt der Autor die Gerinnungszeitbestimmungen selbst durch, die veröffentlichten Angaben sind jedoch derart unvollständig und widersprechend, daß sie keine Schlußfolgerungen gestatten; sie werden von uns weiter hinten im besonderen Kapitel (Frage der haemophilen Blutungserscheinungen bei den Frauen aus dem Bluterstamm von Tenna) eingehend besprochen.

In Anlehnung an HOESSLY-HAERLE (1930) glaubt der Autor, bei den zur Zeit seiner Bestandesaufnahme bereits verstorbenen, wie auch bei den lebenden Konduktorinnen Blutungstendenzen nachweisen zu können. Diese Tendenz können wir jedoch für das gleiche Beobachtungsgut anhand von langjährigen Beobachtungen und eindeutigen Ergebnissen der gerinnungsphysiologischen Untersuchungen *mit Entschiedenheit bestreiten*.

PIANTA bringt in seiner Arbeit 4 genealogische Tafeln, in welchen er die von ihm beschriebenen Bluter 3 bis 4 Generationen mütterlicherseits zurückverfolgt, ohne sie jedoch mit dem von früheren Autoren angegebenen Stammbaum der Bluter von Tenna zu verbinden. Wahrscheinlich deshalb wird in 2 der 4 veröffentlichten Nachfahrentafelausschnitten jeweils eine Generation übersprungen. Eine Verbindung seiner «Teilstämme» mit dem gesamten Stammbaum war wohl ursprünglich vom Autor geplant gewesen, denn er schreibt (S.195) «Sie (die Konduktorinnen, Verf.) sind im Hauptstamme mit roter Farbe bezeichnet»; ein solcher Hauptstamm ist jedoch in der Arbeit nirgends zu finden.

Das Material von PIANTA wurde 1954 von Prof. emer. Dr. med. A. FONIO, Chur, in seine Monographie über die Bluterstämme der Schweiz übernommen. FONIO bringt die Angaben von PIANTA in abgekürzter Form, ohne sie zu berichtigen oder zu vervollständigen, doch mit einigen Mißdeutungen (Druckfehler?) wieder. Im Gegensatz zur Aussage von PIANTA, daß es ihm nicht möglich war, alle Nachkommen der Bluter von Tenna zu erfassen, sagt FONIO in seiner Einleitung, «alle noch lebenden Bluter aufgeführt» zu haben. Diese Behauptung stimmt auf jeden Fall für die Tenner Bluter nicht, da er von den 1954 lebenden 13 nur 8 erfaßte. Daraus ergaben sich aber weitere Ungenauigkeiten, da die veröffentlichten Angaben zur vergleichenden Berechnung der haemophilen Mutationsrate in der Schweiz (VOGEL, 1955a) benützt worden sind.

Wir möchten hier nicht näher auf die genetischen Betrachtungen eingehen, die PIANTA und FONIO anhand ihres Materials aufgestellt haben, da beide Autoren die diesbezüglichen Erkenntnisse unseres Jahrhunderts unbeachtet lassen. Im übrigen möchten wir für die Arbeit von FONIO auf die eingehende Kritik von VOGEL (1955b) hinweisen.

3. Die Durchführung der Bestandesaufnahme und Versuch der Erfassung sämtlicher **Nachkommen** des ersten bekannten **Stammelternpaares** der **Bluter** von Tenna

A. Genealogische Nachforschungen zum Aufstellen einer vollständigen Nachfahrentafel des ersten bekannten Stammelternpaares der Bluter von Tenna

Den Ausgangspunkt unserer Bestandesaufnahme bildete die Arbeit von A. HOESSLI (1885), in welcher die damals bekannten Tenner Bluter mit voller Namengebung angeführt sind. Die darin enthaltenen Angaben, zusammen mit unserem genealogischen Material aus den sero-anthropologischen und genetischen Untersuchungen bei den Walsern (siehe Einleitung), ermöglichten uns die Identifizierung der nur mit Initialen bezeichneten Genealogien des Tenner Bluterstammes von HOESSLY-HAERLE (1930), welche bis an das Stammelternpaar Albrecht WALTHER (II.2) und Ursula BUCHLI (II.3) aus der 2. Hälfte des 17. Jahrh. zurückreichen. Nach Feststellung der Identität dieses Stammelternpaares versuchten wir vorerst seine *Vorfahren oder Geschwisterschaften* anhand der vorhandenen genealogischen Originalquellen, d.h. der Kirchenbücher und der Gemeindearchive, festzustellen, was sich aber als unmöglich erwies. Sodann wurde an das Aufstellen einer möglichst vollständigen Nachfahrentafel dieses ersten bekannten Stammelternpaares geschritten, um auf diesem Wege alle auffindbaren Nachkommen des Bluterstammes von Tenna zu erfassen.

Zu diesem Zwecke wurden zunächst alle Posten aus den Kirchenbüchern von Tenna, Safien und Versam aufgenommen und die dort aufgefundenen Nachfahren des Stammelternpaares in einer genealogischen Tafel zusammengestellt. Die Kirchenbücher dieser 3 Orte lieferten Angaben über den Hauptstamm der gesamten Nachfahrentafel des Bluterstammes von Tenna und zugleich über die meisten Bluterfälle bis Mitte des 19. Jahrh.; die frühesten Eintragungen sind in den Sterberegistern zu finden und reichen bis um 1600 zurück.

Von den so gefundenen Angaben ausgehend, dehnten wir unsere Nachforschungen auf die Kirchenbücher zahlreicher weiterer Gemeinden und schließlich, für die Zeit nach 1860, auf die Bürgerregister (siehe weiter unten) aus.

Die Bestandesaufnahme anhand der Kirchenbücher stieß auf folgende Schwierigkeiten:

- Die Eintragungen waren in einigen Fällen durch mehrjährige Lücken unterbrochen.

- Die Identifizierung der gleichen Personen in den Geburts-, Ehe- und Sterberegistern war erschwert durch die sehr starke Verbreitung der gleichen Vor- und Geschlechtsnamen, durch das Fehlen der Geburtsdaten in den Ehe- und Sterberegistern und durch das oftmalige Eintragen der verheirateten Frauen in den Sterberegistern nur mit ihren Mädchennamen.
- Die Abwanderung einer Person, eine auswärtige Eheschließung oder ein auswärts erfolgter Todesfall wurden nur selten in den alten Kirchenbüchern vermerkt.

Um diesen Schwierigkeiten zu begegnen, war es nötig, den Inhalt ganzer Kirchenbücher aufzunehmen, um dann durch Zusammenstellen der Angaben aus den Geburts-, Ehe- und Sterberegistern die fehlenden Auskünfte zu eruieren. Manchmal war dies auch nur dank zusätzlicher Kirchenbuchaufzeichnungen, wie Wohnort der Familie. Beruf des Vaters usw., oder aber durch Zuziehen von Urkunden aus den Archiven möglich. Es ist uns dabei u. a. die im Bündnerland sehr streng eingehaltene Tradition der Vornamengebung behilflich gewesen, indem der erste Sohn nach seinem Großvater väterlicherseits, die erste Tochter nach ihrer Großmutter mütterlicherseits, der zweite Sohn nach seinem Großvater mütterlicherseits und die zweite Tochter nach ihrer Großmutter väterlicherseits benannt wurden; diese Tradition wurde von uns aber lediglich als Hinweis für weitere Nachforschungen, jedoch nie als Beweis angesehen.

Die fehlenden Angaben über die abgewanderten oder nach auswärts verheirateten bzw. dort verstorbenen Personen konnten zum Teil in den Kirchenbüchern anderer Gemeinden gefunden werden; die Kenntnis der historischen Beziehungen zwischen den Gemeinden ist für das Anstellen der Nachforschungen unerlässlich gewesen.

Bei allen aus den Kirchenbüchern vor 1837 übernommenen Angaben sind anstelle der Geburtsdaten die Taufdaten und anstelle der Sterbedaten die Begräbnisdaten zu verstehen; es ergibt sich dadurch nur eine geringe Ungenauigkeit, da es im Bündnerland Brauch gewesen ist, die Neugeborenen in den ersten Lebenstagen zu taufen.

Die Angaben von der Mitte des 19. Jahrh. an wurden den Bürgerregistern entnommen.

Alle Schweizer und Schweizerinnen sind Bürger einer Heimatgemeinde, und zwar unabhängig von ihrem Wohnort und Geburtsort. Das Bürgerrecht wird auf die Nachkommen vererbt; bei der Heirat erhält die Frau das Bürgerrecht ihres Gatten, außereheliche nicht legitimierte Kinder erhalten das Bürgerrecht ihrer Mutter, Ausländer werden durch Erwerb eines Gemeindebürgerrechtes zu Schweizer Bürgern.

Mit dem Bürgerrecht sind seit jeher gewisse Vorteile verbunden, wie z. B. Anteil- bzw. Nutzungsrecht am Gemeindebesitz wie Wald, Weide und Alp, Anrecht auf Armenunterstützung u.a.m. (vgl. P. LIVER bei ZÜRCHER, 1957). Die Bedeutung sowie die Vererbbarkeit des Bürgerrechtes brachte es mit sich, daß entsprechende Urkunden und Aufzeichnungen bei Privaten und in den Gemeindearchiven sorgfältig aufbewahrt wurden.

1860 wurden in allen Bündner Gemeinden die Bürgerregister eingeführt. Sie enthalten die Angaben über Geburten, Eheschließungen und Todesfälle aller Gemeindebürger. Den gesetzlichen Vorschriften entsprechend werden diese Register sehr genau von den Zivilstandsämtern geführt und stellen eine zuverlässige Quelle für genealogische Nachforschungen dar.

Da in den Bürgerregistern nur die Manneslinie verfolgt wird, mußten die Todesdaten der verheirateten Frauen sowie die Angaben über ihre Nachkommen stets in den Bürgerregistern der Ehemänner gesucht werden, wodurch das Verfolgen der Frauenlinien besonders zeitraubend gestaltet wurde.

Die Bestandesaufnahme für die Zeit nach 1860 war zwar dank der Bürgerregister erleichtert, doch wurde die Durchführung einer vollständigen Erfassung durch die hohe Zahl der Nachkommen und durch die geographische Streuung ihrer Bürgerorte bedeutend erschwert.

B. Umfang der Erfassung der Nachkommen des ersten bekannten Stammelternpaares der Bluter von Tenna

Wir stellten uns als Aufgabe, eine vollständige Nachfahrentafel des ersten bekannten Stammelternpaares der Tenner Bluter aufzustellen; sie sollte alle Nachkommen dieses Elternpaares in männlicher und in weiblicher Linie samt allen Angeheirateten enthalten.

Durch das Erfassen der 3072 Personen, verteilt auf 13 Generationen (vgl. Tab. 3), gelang es uns, dieses Vorhaben fast vollständig zu erfüllen.

Die I. Generation unserer genealogischen Erfassung wird von den Eltern (I. 1 und I. 2) des Stammvaters Albrecht WALTHER (II. 2) gebildet. Somit gehört eigentlich die I. Generation nicht zu der *Nachfahrentafel* des ersten bekannten Stammelternpaares (II. 2 und II. 3), und wir führen sie nur vollständigkeithalber auf; das Ehepaar I. 1 und I. 2 stellt die einzigen eruierbaren Vorfahren des Stammelternpaares der Bluter von Tenna dar.

In den Kirchenbüchern ließen sich auch keine Geschwister des Stammelternpaares mit Sicherheit feststellen.

Tab. 3. Gesamtzahl aller genealogisch erfaßten Personen des Bluterstammes von Tenna, eingeteilt nach Generationen, Teilen der Nachfahrentafel und Geschlecht (siehe Bemerkung (2) und (3) zu Tab. 1, S. 7)
 All Tenna Hemophiliacs and Descendants recorded, grouped by generations, parts of Table of Descendants and by sex (see notes (2) and (3) concerning Tab. 1, p. 7)

Gene- ration	Nachfahrentafel Teil A Part A of Table of Descendants				Nachfahrentafel Teil B Part B of Table of Descendants				Nachfahrentafel Teil C Part C of Table of Descendants				Total nach Geschlecht Totals per sex			
	♂	♀	Ge- schlecht nicht erfaßt	Tot- bzw. Frühgeburt Geschlecht unbekannt	♂	♀	Ge- schlecht nicht erfaßt	Tot- bzw. Frühgeburt Geschlecht unbekannt	♂	♀	Ge- schlecht nicht erfaßt	Tot- bzw. Frühgeburt Geschlecht unbekannt	♂	♀	Ge- schlecht nicht erfaßt	Tot- bzw. Frühgeburt Geschlecht unbekannt
I.	1	1											1	1		2
II.	1	2											1	2		3
III.	4	6		1									4	6	1	11
IV.	1	1														
V.	6	5														
VI.	16	18			11	9			6	6			18	16		34
VII.	41	39			24	31			7	7			37	43		80
VIII.	57	55			41	37			10	9			67	64		131
IX.	69	55			52	49			12	8			105	96		201
X.	89	82			92	82		1	35	34			184	171	2	357
XI.	90	71			135	134			50	50		1	253	239		492
XII.	14	16	1		201	196			71	76		2	361	353	6	720
XIII.	1	1			215	206	2	2	97	88			402	365	2	771
					74	65	8		47	28			135	109	9	253
					9	5							9	6		15
													1578	1472	11	3072

Die gemeinsamen Vorfahren, d.h. die Generationen I., II. und III., werden zu Teil A der Nachfahrentafel gerechnet.
 The common ancestors, e.g. Generations I., II. and III., are included in part A of Table of Descendants.

In der Nachfahrentafel steigt die Zahl der Nachkommen von der III. erfaßten Generation an, um in der XI. Generation ein Maximum zu erreichen und bis in die XIII. wieder abzunehmen. Die X. Generation stellt mit der jüngsten im Jahre 1944 geborenen Person die letzte vollständig erfaßte Generation der Nachfahrentafel dar. Weitere Geburten sind in dieser Generation nicht zu erwarten, da sämtliche Frauen der Eltern-generation (Generation IX) das als Fortpflanzungsgrenze für Frauen angenommene 50. Lebensjahr bereits überschritten haben. Die Generationen XI bis XIII werden noch nach Abschluß unserer Bestandesaufnahme weiter durch Geburten vergrößert. Diese 3 letzten Generationen wurden von uns bis in die Zeitspanne 1952 bis 1956 erfaßt, davon die allermeisten Fälle bis 1955 und alle Bluterfamilien bis Ende 1956 bzw. Mitte 1957.

Im Laufe unserer Nachforschungen mußten wir feststellen, daß ein vollständiges Erfassen *sämtlicher* Nachkommen des Stammelternpaares nicht durchführbar ist.

Eine Anzahl von Personen, deren Geburt in den Kirchenbüchern verzeichnet war, konnte in keinem der eingesehenen Ehe- und Sterberegister wiedergefunden werden, sei es, weil sie abgewandert waren, sei es infolge der in den Registern vorkommenden Lücken. Diese Personen können als *nicht weiter verfolgbar* bezeichnet werden. Für die Zeit nach der Einführung der Bürgerregister im Jahre 1860 sind es die Auswanderer, die den Kontakt mit ihrer Heimatgemeinde nicht mehr aufrechterhielten, wie auch die mit Ausländern verheirateten Frauen, die in den Bürgerregistern *nicht mehr verfolgbar* sind. Es konnten hier jedoch die fehlenden Angaben teilweise von uns bekannten Familienmitgliedern (vgl. Tab. 5) erfragt werden, und zwar vor allem in den Fällen mit vermutlichem Blutererbgang.

Insgesamt gibt es in der ganzen Nachfahrentafel 115 *nicht weiterverfolgbare Personen*.

Nachdem die Nachforschungen für das Aufstellen der Nachfahrentafel bereits 4 Jahre gedauert hatten, beschlossen wir, sie Ende des Jahres 1955 abubrechen, um nicht wieder mit Sammeln der Angaben über die inzwischen erfolgten Geburten, Eheschließungen und Todesfälle bei den anfangs der Bestandesaufnahme erfaßten Personen beginnen zu müssen. In diesem Moment gab es aber in der Nachfahrentafel 108 Personen, die wohl verfolgbar wären, jedoch von uns noch *nicht weiter verfolgt* wurden und auf deren vollständiges Erfassen wir nunmehr verzichtet haben. Es handelte sich dabei fast ausschließlich um Frauen, die außerhalb ihrer Heimatgemeinde geheiratet haben und seither in den Bürgerregistern ihrer Ehe-

Tab. 4 Umfang der Erfassung von sämtlichen Nachfahren des Stammelterns
 Scope of Recorded Descendants, and their Spouses, of First Ancestor

Kategorien der erfaßten Personen Categories of persons recorded		Teile der Nachfahrtentafel Parts of Table of Descendants	I.	II.	III.
Personen, deren ganze Lebensdauer bzw. die Lebensdauer von der Geburt bis zum Zeitpunkt der Bestandesaufnahme 1952-1956 erfaßt wurde Persons followed up from birth to decease or from birth to time of investigation 1952-1956	Ehepaare mit Nachkommen Married couples with descendants	A B C	2 (1)	2 (1)	7 (1)
	Kinderlos gebliebene Ehepaare (inklusive sterile Ehen im Fortpflanzungsalter) Childless couples (including sterile couples of procreative age)	A B C			
	Junge Ehepaare, im Zeitpunkt der Bestandesaufnahme noch kinderlos Young couples, childless at time of investigation	A B C			
	Vor 1952-1956 verstorbene unverheiratete Personen Single persons deceased before 1952-1956	A B C			3
	1952-1956 lebende unverheiratete Personen Single persons alive at time of investigation	A B C			
Nicht weiterverfolgbare Personen Persons recorded at birth, at time of their marriage or emigration but untraceable thereafter	Auswanderer Emigrants	Ehepaare zur Zeit der Auswanderung im Fortpflanzungsalter Married couples of procreative age at time of emigration			
		Ehefrau keine Konduktorin Wife non-carrier	A B C		
	Unverheiratete Personen Single persons	Ehefrau mögliche Konduktorin Wife possible carrier	A B C		
		Keine haemophile Vererbung möglich No hemophilic heredity	A B C		
		Haemophile Vererbung theoretisch möglich, doch nicht aufgetreten Hemophilic heredity theoretically possible but did not occur	A B C		
		Bluter Hemophiliacs	A B C		
		Keine Konduktorin Non-carrier	A B C		
		Mögliche Konduktorin Possible carrier	A B C		
		Sex unknown, no hemophilic heredity	A B C		
	Seit der Eheschließung nicht mehr verfolgbare Paare Couples recorded at marriage, but untraceable thereafter	Ehefrau keine Konduktorin Wife non-carrier	A B C		
		Ehefrau mögliche Konduktorin Wife possible carrier	A B C		

n Tenna, Angeheiratete inbegriffen (siehe Bemerkung (2) und (3) zu Tab. 1, S. 7)

Hemophilacs of Tenna (see notes (2) and (3) concerning Tab. 1, p. 7)

Einteilung in Generationen Division into generations								Zusammenfassung der einzelnen Kategorien Totals			
I.	VII.	VIII.	IX.	X.	XI.	XII.	XIII.				
(12) (20) (6)	46 (23) 61 (32) 14 (7)	52 (26) 94 (51) 38 (20)	64 (33) 156 (79) 60 (31)	103 (52) 224 (114) 93 (47)	14 (7) 98 (49) 56 (28)	2 (1) 12 (6)		328 (164) 725 (372) 283 (145)	1336 (681)		
(1) (4) (2)	11 (6) 7 (5)	7 (4) 8 (4) 10 (5)	15 (8) 16 (8) 8 (4)	8 (4) 18 (9) 9 (5)	2 (1) 4 (2)			43 (23) 66 (35) 34 (22)	143 (80)	1515 (770)	
				4 (2) 8 (4) 4 (2)	12 (6) 6 (3)	2 (1)		4 (2) 20 (10) 12 (6)	36 (18)		2849
	17 23 5	26 51 19	26 57 24	29 58 25	14 21 10	2 7 2		123 261 103	487		
			1 18 3	19 59 13	118 288 97	27 118 71	1 14	166 497 184	847	1334	
	6 (3)	4 (2)	4 (2)		2 (1) 2 (1)			4 (2) 12 (6) 2 (1)	18 (9)	18 (9)	
									0		
I	4 2	12 3		1				16 4 3	23		
	3 { 180 181 241							3	7		
	2 { 346 347	2 { 414 415						4			
	11)							1	1	63	
	4 1	3						7 1	8	45	
	3 { 236 239 240							3	4		
	1 { 345							1			
					2			2	2		
			6 (3)	2 (1)	2 (1)			8 (4) 2 (1)	10 (5)		
	2 (1) 186			2 (1) 394		2 (1) 93		6 (3)	6 (3)	16 (8)	
121	191	332	478	679	748	245	15				

Tab. 4 Umfang der Erfassung von sämtlichen Nachfahren des Stammelternpaares
Scope of Recorded Descendants, and their Spouses, of First Ancestors

Kategorien der erfaßten Personen Categories of persons recorded		Teile der Nachfahrentafel Parts of Table of Descendants				
				I.	II.	III.
Übertrag Forward				2	2	10
Nicht weiterverfolgbare Personen Persons recorded at birth, at time of their marriage or emigration, but untraceable thereafter	Seit der Geburt nicht mehr verfolgbare Personen Single persons recorded at birth, but untraceable thereafter	O ₁	Keine haemophile Vererbung möglich No hemophilic heredity	A B C		
			Haemophile Vererbung möglich Hemophilic heredity virtually possible	A B C		
			Bluter Hemophiliacs	A B C		
			Keine Konduktorin Non-carrier	A B C	1	1
		O ₂	Mögliche Konduktorin Possible carrier	A B C		
Nicht weiterverfolgte Personen Persons recorded at birth or at time of their marriage but follow up discontinued at close of investigation	Seit der Eheschließung nicht mehr verfolgte Ehepaare Married couples not followed up after time of marriage		Ehefrau keine Konduktorin Wife non-carrier	A B C		
			Ehefrau mögliche Konduktorin Wife possible carrier	A B C		
	Seit der Geburt nicht mehr verfolgte Personen Single persons not followed up after time of birth	O ₁	Keine haemophile Vererbung möglich No hemophilic heredity	A B C		
			Haemophile Vererbung möglich Hemophilic heredity virtually possible	A B C		
		O ₂	Bluter Hemophiliacs	A B C		
			Keine Konduktorin Non-carrier	A B C		
			Mögliche Konduktorin Possible carrier	A B C		
Personenzahl pro Generation (vgl. Tab. 3) Number of persons per generation (cf. Tab. 3)				2	3	1

¹⁾Bluter B VIII. 265 siehe spezieller Teil der Arbeit.

186 Standortnummer in der Nachfahrentafel (siehe auch Tafel I S. 30).

Die gemeinsamen Vorfahren, d.h. die Generationen I., II. und III., werden zu Nachfahrentafel Teil A gerechnet.

() Jede Person ist in der Tabelle nur 1 Mal aufgeführt; in Klammern ist die Zahl der Eben mit Berücksichtigung der Wiedervermählungen gegeben, z.B. «Kinderlos gebliebene Ehepaare», Nachfahrentafel Teil B, Generation VII. 7 (5) setzt sich zusammen aus: 1 Ehepaar, 2 E eines zweimal verheirateten Mannes, 1 kinderlos verstorbene Frau, deren Mann in einer zweiten Ehe Kinder gezeugt hat und deshalb unter «Ehepaare mit Nachkommen» berechnet wurde, wie auch ein kinderlos verstorbener Mann, dessen Witwe in einer zweiten Ehe Kinder und ebenfalls unter «Ehepaare mit Nachkommen» berechnet ist.

Unverheiratete mit illegitimen Kindern sind als Einzelpersonen berechnet.

Hemophiliacs of Tenna (see notes (2) and (3) concerning Tab. 1, p. 7)

(*) Hemophiliac B VIII. 265 see descriptive part of study.

186 Location Number in Table of Descendants (see also Tafel 1 on page 30).

The common ancestors, i.e. generations I., II. and III., are comprised in part A of descendants' table.

(1) Each person is recorded but once, in brackets are the numbers of marriages including remarriages, e.g., "(childless couples", descendants table part B, generation VII. 7 (5) is composed of: 1 married couple, 2 marriages of a man who married twice, 1 deceased childless woman whose husband had children with his second wife and is recorded in "Married couples with descendants", and 1 deceased man with no descendants, whose widow bore children in her second marriage and is recorded in "Married couples with descendants".

Single women with illegitimate children are recorded as unmarried persons.

Tafel 1 NICHT WEITERVERFOLGBARE UND NICHT WEITERVERFOLGTE PERSONEN MIT THEORETISCH MOEGLICHER HAEMOPHILIEVERERBUNG, DARSTELLUNG ZU TAB. 4 AUSZUG AUS DER NACHFAHRENTAFEL DES BLUTERSTAMMES VON TENNA

Unter den Geschwisterschaften sind nach Geburtsjahren geordnet angegeben. theoretisch mögliche Haemophiliefälle (Standortnummern wie in Tab. 4), theoretisch mögliche Konduktoren (Standortnummern wie in Tab. 4), jeweilige Konduktorenverfahren und die für die Wahrscheinlichkeitsberechnung (siehe S. 51) in Frage kommenden Personen.

Dick gezeichnet: Möglicher Vererbungsweg für alle Fälle mit Möglichkeit von Weitervererbung der Haemophilie
Dunn gezeichnet: Lediglich zur Schilderung der Wahrscheinlichkeitsberechnung angegebene Fälle, zusätzlich die Auswanderer C IX 414 und C IX 415 mit ihren weiblichen Vorfahren

☒ sichere Konduktorin
☐ mögliche Konduktorin

78 Standortnummer in der Nachfahrenstafel
 1795 Geburtsjahr
 1 Todestjahr, wenn nicht angegeben 1956 am Leben
 † als Neugeborenes gestorben
 Mögliche Konduktoren: 1 = nicht weiterverfolgbar, † = nicht weiterverfolgt, ‡ = ausgewandert
 21,4% Wahrscheinlichkeit in % für das Vorhandensein des Haemophiliegens (siehe S. 51)

☒ Vollständigkeitshalber angegebene männliche Personen, die für die Wahrscheinlichkeitsberechnung nicht berücksichtigt wurden, da sie nicht mit Sicherheit als nicht-Haemophile vor dem 6. Lebensjahr ohne bekannte haemophile Manifestation verstorben sind
☒ Auswanderer: in allen 7 Fällen haemophile Vererbung theoretisch möglich, jedoch nicht aufgetreten, keine Blutungserscheinungen bis zur Auswanderung, bzw. auch nachher laut Familienanamnese

VIRTUALLY POSSIBLE HAEMOPHILIC HEREDITY AMONG UNTRACEABLE AND NOT FOLLOWED UP PERSONS FROM TAB. 4, EXTRACT FROM DESCENDANTS TABLE OF HAEMOPHILIACS OF TENNA

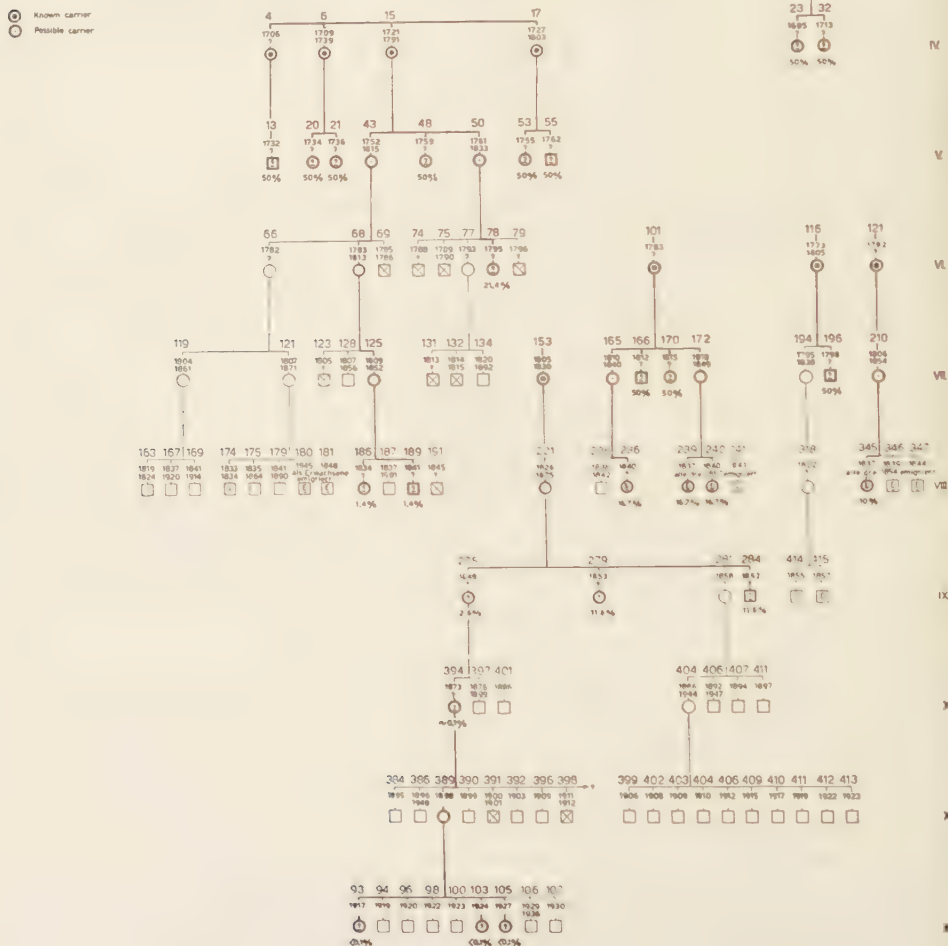
Among the stoppage are listed in rank of birth: virtually possible haemophiliacs (Location Numbers as in tab. 4), virtually possible carriers (Location Numbers as in tab. 4), carrier-ancestors of recorded cases, and persons relevant for calculation of probabilities (see p. 51)

Thick printing: Possible way of transmission for all cases with possibility of transmission of haemophilia
Thin printing: Cases used for calculation of probabilities only (see p. 51)

78 Location number in descendants' table
 1795 Year of birth
 † Year of death, if not stated, person alive in 1956
 ‡ deceased before completion of 1st year of life
 Possible conductor: 1 = untraceable, † = not followed up, ‡ = emigrants
 21,4% Probability in % for presence of gene of haemophilia (see p. 51)

☒ Males listed for the sake of completeness but not introduced into calculation of probabilities, because of death in their non-haemophilic status, viz.: children deceased before completion of 1st year of life, haemophiliacs might have passed unrecognised – persons whose year of death is unknown, death may have occurred at adult age
☒ Emigrants: in all 7 cases haemophilic heredity virtually possible but not occurring, no haemophilic manifestations before the time of emigration and/or after it, as stated by relatives

☒ Known carrier
☐ Possible carrier



Anmerkung zur Legende: Lies S. 53 statt S. 51

männer aufgeführt wurden. Da wir nicht alle Gemeinden aufsuchen konnten, um die Register einzusehen, mußten wir einen Teil unserer Nachforschungen auf dem Korrespondenzwege mit den Zivilstandsämtern durchführen, was sich in vielen Fällen als sehr zeitraubend erwies. Unser Verzicht auf die Weiterverfolgung der 108 Personen ist unter den gegebenen Umständen unumgänglich gewesen.

Der Umfang unserer Erfassung der Nachkommen des Stammelternpaares und die Wahrscheinlichkeit von Weitervererbung der Haemophilie bei den *nicht weiter verfolgten* und den *nicht weiter verfolgten* Nachkommen ist aus Tab. 4 und Tafel 1 ersichtlich.

4. Die Durchführung der Bestandesaufnahme und der Umfang der Erfassung von **Blutern** unter den erfaßten Nachkommen des ersten bekannten Stammelternpaares der Bluter von Tenna

Sämtliche Bluter aus dem Stamm von Tenna mußten unter den Nachkommen des Stammelternpaares (II. 2 und II. 3) aufgetreten sein. Somit sind sie alle in der von uns aufgestellten Nachfahrentafel erfaßt, insoweit diese auf Vollständigkeit Anspruch erheben darf (vgl. Tab. 4). Um einen Überblick über den Umfang der Erfassung dieser Bluter zu gewinnen, müssen noch folgende Fragen beantwortet werden:

- A. Nach welchen Richtlinien wurde jeweils die Haemophiliediagnose gestellt?
- B. Sind alle Bluter in der Nachfahrentafel als solche erfaßt worden?
- C. Können Bluter unter den *Vorfahren* der Stammutter (II. 3) und unter ihren *Geschwistern* und deren Nachkommen vermutet werden?

Die Antworten auf diese Fragen und ihre Genauigkeit ergeben sich aus dem nachstehend geschilderten Gang unserer Nachforschungen.

A. Angewandte Richtlinien für die Diagnose der Haemophilie

1) Diagnose bei den während der Bestandesaufnahme 1952–1956 untersuchten Männern.

Die Diagnose der Haemophilie, wie auch ihre Unterscheidung von anderen haemorrhagischen Diathesen, gründen auf den Besonderheiten des klinischen Krankheitsbildes, des gerinnungsphysiologischen Laboratoriums-

befundes und der *Erblichkeit* des Leidens. Diese 3 Gesichtspunkte lagen auch den Nachforschungen unserer Bestandesaufnahme zugrunde.

Das klinische *Krankheitsbild* der Probanden wurde nach dem folgenden Frageschema erfaßt:

- 1) Blutungen nach Verletzungen:
Verlauf? Dauer?
Wann und wo behandelt?
Vorkommen von Nachblutungen (nach vorübergehendem Wundverschluß)?
- 2) Suffusionen (Blutunterlaufungen):
Oft? Selten? Größe?
Unmittelbare auslösende Ursachen?
- 3) Blutungen in die Weichteile (Muskulatur):
Verlauf?
Unmittelbar auslösende Ursache?
Wann und wo behandelt?
- 4) Blutungen aus dem Mund:
Beim Zahnen bzw. bei Zahnwechsel, bei Zahnextraktion?
Aus dem Zahnfleisch:
an einer verletzten Stelle?
parenchymatös?
Verlauf? Dauer?
Wann und wo behandelt?
- 5) Nasenblutungen:
Verlauf? Dauer?
Wann und wo behandelt?
- 6) Gelenkblutungen:
An welchen Gelenken?
Verlauf?
Wann und wo behandelt?
- 7) Viscerale Blutungen:
Blut im Harn?
Blutbrechen?
Blutiger oder schwarzer Stuhl?
Andere Angaben über viscerale Blutungen?
- 8) Blutungen im Zentralnervensystem:
Lokalisation?
Verlauf?
Wann und wo behandelt?

- 9) Andere als unter 1 bis 8 aufgezählte Blutungen?
 Lokalisation?
 Verlauf? Dauer?
 Wann und wo behandelt?
- 10) Wann ist die abnorme Blutungsbereitschaft das erste Mal aufgetreten?
 Auf welche Art?
 Verlauf? Dauer?
 Wo behandelt?
- 11) Haemophiler Erbgang:
 Bei Vorfahren?
 Bei Nachkommen?
 Bei Geschwistern und ihren Nachkommen?
- 12) Gegenwärtiger Status:
 Sind die unter 1 bis 9 aufgezählten Haemophiliesymptome oder deren Folgen vorhanden?
 Welche?

Bei allen Probanden, d.h. bei allen lebenden möglichen Trägern des Haemophiliegens (vgl. Tafel 6), wurde anhand des Frageschemas nach Blutungserscheinungen geforscht. Dadurch ergab sich bei allen Bluterfällen eine genaue Anamnese seit der ersten Manifestation des Leidens bis Ende 1956 bzw. Mitte 1957. Die anamnestischen Angaben setzen sich, zusätzlich zu unseren eigenen Beobachtungen, aus Mitteilungen der behandelnden Ärzte und Spitäler und aus den Literaturangaben über einige früher bereits beschriebene Fälle zusammen (vgl. Tab. 13). Alle Anamnesen sind in abgekürzter Form im speziellen Teil dieser Arbeit wiedergegeben.

Anhand des klinischen Symptomenkomplexes konnte bei 12 Probanden eine sichere Haemophiliediagnose gestellt werden.

Die Ergebnisse der *gerinnungsphysiologischen Laboratoriumsuntersuchungen* verdanken wir der Mitarbeit von Dr. M. GEIGER aus dem Gerinnungsphysiologischen Labor von Prof. F. KOLLER des Kantonsspitals Zürich. Die angewandten Untersuchungsmethoden gestatteten nebst dem Nachweis der Haemophilie auch die Differentialdiagnose des Haemophilietypus, wie dies hier später beschrieben wird.

In Anbetracht der durchgeführten zuverlässigen Laboratoriumsuntersuchungen wurde auf die Bestimmung der Gerinnungszeit verzichtet, besonders da ihre große Variationsbreite bei Haemophilie (SCHLOESSMANN, 1930) bekannt ist und auch neuerdings vollständig normale Werte bei Blutern beschrieben wurden (MERSKEY, 1951a, 1951b). Die im speziellen

Teil dieser Arbeit bei einigen Bluterfällen angegebenen Gerinnungszeitbestimmungen wurden aus den uns übermittelten Krankengeschichten vollständigshalber übernommen.

Die Laboratoriumsuntersuchungen von GEIGER konnten aus äußeren Gründen nur bei 9 der 12 klinisch diagnostizierten Bluter durchgeführt werden. Sie bestätigen in allen diesen Fällen den klinischen Befund. Zusätzlich konnte bei einem Kind (B XI. 507), das keine klinischen Blutungserscheinungen manifestiert hat, ein gerinnungsphysiologisch haemophiler Befund erhoben werden, was die Zahl der in den Jahren 1952 bis 1956 lebenden Bluter auf 13 erhöht.

Was die *Erblichkeitsverhältnisse* anbetrifft, so sind sie aus unserer Nachfahrentafel für alle in den Jahren 1952 bis 1956 lebenden Bluter ersichtlich. Der geschlechtsgebunden-rezessive Erbgang läßt sich bei allen diesen Bluterfällen nachweisen, wodurch die klinischen und gerinnungsphysiologischen Diagnosen der Haemophilie bestätigt werden.

2) Diagnose bei den vor der Bestandesaufnahme 1952–1956 verstorbenen Männern.

Hier standen uns nur *katamnestische Angaben* über das Krankheitsbild und der *Nachweis des haemophilen Erbganges* als diagnostische Mittel zur Verfügung. Sie wurden anhand unseres eingangs wiedergegebenen Fragechemas zusammengestellt und ausgewertet und sind im speziellen Teil dieser Arbeit kurz zusammengefaßt. Ihre Ausführlichkeit und Genauigkeit war sehr verschieden und beschränkte sich bei einer Anzahl früher Fälle nur auf einen knappen Vermerk über den Verblutungstod.

Die *Differentialdiagnose* gegenüber anderen haemorrhagischen Diathesen wurde erst in die persönlichen Untersuchungen von HOESSLY-HAERLE (1930) mit einbezogen. HOESSLY (1885), der keinen Bluter persönlich untersuchen konnte und sich mit der Aufnahme fremder Berichte begnügen mußte, beschränkt sich auf die allgemein gehaltene Bemerkung «Scorbut, purpura haemorrhagica, sind ganz gewiß auf Tenna nie vorgekommen». Ähnlich GRANDIDIER (1877), der zwar in seiner Monographie ein besonderes Kapitel der Differentialdiagnose von Haemophilie gegenüber Rheumatismus, Scorbut und Purpura haemorrhagica nach WERLHOF widmet, sich jedoch in seiner Beschreibung der Bluter von Tenna mit dem Vermerk begnügt: «Scorbut, purpura haemorrhagica und organische Herzkrankheiten hatte VIELI dort nicht beobachtet, obgleich acuter Gelenkrheumatismus häufig vorkommt». Seine Angaben entnahm GRANDIDIER

den persönlichen Mitteilungen von VIELI, die er für die erste Ausgabe seiner Monographie (1855a) erhalten hat. In seiner eigenen Veröffentlichung befaßt sich VIELI (1846) mit der Differentialdiagnose überhaupt nicht, ebensowenig einige Jahre früher THORMANN (1837), in seiner in der Literatur chronologisch ersten Beschreibung der Bluter von Tenna.

Wenn uns somit bei den Autoren des 19. Jahrh. die differentialdiagnostischen Untersuchungen fehlen, so kann dennoch anhand der angegebenen Katamnesen jeweils eine weitgehend zuverlässige Haemophiliediagnose gestellt werden. Sogar bei Fällen, die ohne katamnestische Angaben bei den ersten Autoren und in den Kirchenbüchern nur kurz als Bluter bezeichnet sind, besteht wenig Zweifel an der Richtigkeit dieser Diagnose. Denn schon diese frühesten, kurzen Beschreibungen der Bluterfälle (vgl. spezieller Teil dieser Arbeit) sind meistens für die Haemophilie pathognomonisch und erwecken den Eindruck, daß der haemophile Symptomenkomplex in Tenna bereits frühzeitig erkannt worden ist. Das Erkennen des Krankheitsbildes mußte ja auch durch das gehäufte Auftreten innerhalb der kleinen Bevölkerung stark gefördert werden.

Es kann somit auch mit großer Wahrscheinlichkeit angenommen werden, daß die in den Kirchenbüchern eingetragenen und den beschreibenden Ärzten von der Bevölkerung mitgeteilten Bluterfälle tatsächlich an Haemophilie und nicht an Folgen von zufälligen Verletzungen gelitten haben. Wir können uns hier der folgenden Stellungnahme von HOESSLI (1885) ganz anschließen:

«Diese Citate aus den alten Kirchenbüchern, von verschiedenen Beobachtern (verschiedene Pfarrer, Verf.) herrührend, verfehlen nicht, unsere Aufmerksamkeit in hohem Grade zu fesseln und drängen uns mit Macht die Frage auf, ob wir es in den vorliegenden Fällen mit Blutern zu thun haben oder nicht? Es ist im höchsten Grade unwahrscheinlich, daß es sich in den obgenannten vier Fällen um Blutungen handelt, welche die Folge einer größeren Verletzung gewesen sind, denn dann hätten die Beobachter es sicherlich nicht unterlassen, die Art desselben, wenigstens mit ein paar Worten, genauer zu bezeichnen, wie dies in der That nach den Registern (Sterberegister der Kirchenbücher, Verf.) zu schließen, mehrfach vorgekommen ist. So sind z. B. schwere Verletzungen im Walde oder auf den Alpen etc., die den Tod des Betroffenen verursachten, stets genauer beschrieben.»

Auch die Vererbung des Leidens war zur Zeit der Berichte von THORMANN (1837) und von VIELI (1846) in Tenna gut bekannt; THORMANN schreibt darüber:

«Merkwürdig ist die Fortpflanzung dieser Disposition zu starken Blutungen (idiosyncrasia haemorrhagica) auf die nachkommenden männlichen Verwandtschaftsglieder, indem die weiblichen Individuen der Verwandtschaft diese Idiosyncrasie nicht besitzen, sondern auf die Söhne übertragen, und der Vater somit dieselbe durch die Tochter seinem männlichen Enkel mittheilt.»

Ähnlich bei VIELI (1846) und noch besonders eingehend in seinen Berichten an GRANDIDIER (1855a):

«Bezüglich der erblichen Fortpflanzung der Krankheit gilt in Tenna das Gesetz, daß die weiblichen Glieder der dortigen Bluterfamilien nicht selbst an Blutungen leiden, dagegen die Diathese fortpflanzen, während es sich bei den männlichen Blutern umgekehrt verhält, erstere werden deshalb dort Conductoren genannt.»

Somit kann behauptet werden, daß die Einwohner von Tenna die Haemophilie schon am Anfang des 19. Jahrh. als eine nosologische Einheit in ihrer Symptomatologie und Vererbung kannten. Folglich können auch die dortigen Angaben über die Bluter als weitgehend zuverlässig angesehen werden.

Im übrigen wird die Diagnose aller dieser Fälle durch den geschlechtsgebunden-rezessiven Erbgang ihres Leidens bestätigt (Ausnahmefall: der sporadische Bluter A IX.10). Auch ist bei ihnen die Wahrscheinlichkeit der Haemophilievererbung von ihren nahen Blutervorfahren bedeutend größer als das zufällige Auftreten von anderen haemorrhagischen Diathesen.

In Anbetracht aller dieser Überlegungen bezeichnen wir als Haemophile alle Personen, die in den Kirchenbüchern und bei den früheren Autoren als Bluter oder an Verblutungstod verstorbene angegeben sind.

Konsequenterweise wird auch der Ausnahmefall A IX.10 (siehe spezieller Teil dieser Arbeit) infolge seiner Blutungsbereitschaft und seinem Verblutungstod von uns als Bluter bezeichnet, wenn auch bei seinen Vorfahren kein haemophiler Erbgang nachgewiesen werden konnte und bei ihm selbst außer den starken Nasenblutungen keine anderen Blutungserscheinungen überliefert sind.

In diesem Zusammenhang soll auch die Frage der von HOESSLY-HAERLE (1930) angegebenen «rudimentären Bluter» besprochen werden.

HOESSLY-HAERLE nennt 6 solche Fälle, darunter den letztbesprochenen A IX.10, der von uns in Anbetracht der hier bereits angegebenen diagno-

stischen Richtlinien als Bluter angesehen werden muß. Er wird von HOESSLY-HAERLE als «rudimentär» bezeichnet, weil unter seinen Vorfahren keine Haemophiliefälle bekannt sind, eine Stellungnahme, die in Anbetracht der genetischen Erkenntnisse dahinfällt.

Die übrigen 5 Diagnosen der «rudimentären Haemophilie» (A VII. 7, B VIII. 224, B IX. 308, B X. 531, C VIII. 328) beruhen zum Teil auf Indizien, die wir nicht als genügend beurteilen und die im speziellen Teil dieser Arbeit eingehend besprochen werden, und zum Teil auf einer von HOESSLY-HAERLE (S. 344–348) aufgestellten «Vererbungsformel der Haemophilie... mit Abschwächung des haemophilen Gens bei gleichzeitig atypischem Erbgang», die wir nicht als richtig anerkennen können. Somit betrachten wir diese 5 Probanden als überhaupt nicht haemophil und finden in der ganzen Nachfahrentafel des Bluterstammes von Tenna keine Berechtigung für das Aufstellen eines neuen nosologischen Begriffes der «rudimentären Bluter».

3) Frage der haemophilen Blutungserscheinungen bei den Frauen aus dem Bluterstamm von Tenna.

Weder die Kirchenbücher noch die Autoren des 19. Jahrh. erwähnen Blutungserscheinungen bei Frauen aus dem Bluterstamm von Tenna. Die entsprechenden Stellungnahmen von THORMANN (1837) und von VIELI (bei GRANDIDIER. 1855a und 1877) sind bereits aus den hier wiedergegebenen Auszügen (S. 35 und S. 36) ihrer Veröffentlichungen ersichtlich.

In der uns zur Verfügung stehenden II. Auflage der Monographie von GRANDIDIER (1877), die jedoch nach BULLOCH und FILDES (1912) in bezug auf die Angaben über die Bluter von Tenna mit der I. Auflage von 1855 identisch ist, schreibt zwar der Autor:

«Die Frauen (aus den Bluterfamilien, Verf.) leiden nur zuweilen an profuser Menstruation und starken Blutungen nach der Entbindung, auch glaubt Vieli bei ihnen eine Disposition zu Abortus und Hirncongestion bemerkt zu haben.»

Diese Symptome legt jedoch VIELI keineswegs im Sinne der weiblichen Haemophilie aus, deren Vorkommen in Tenna er einige Zeilen weiter unten ausdrücklich ablehnt:

«Er bestätigt nach den Aussagen sämtlicher Einwohner von Tenna, dass von jeher nur die Knaben einer Bluterfamilie dieser Krankheit unterworfen sind, die Mädchen aber nur als Trägerinnen des Leidens, nach dortigem Ausdrucke als Conductoren gelten.»

ferner:

«... es existiert kein sicher verbürgtes Beispiel, daß Töchter einer Bluterfamilie selbst bluteten.»

Auch GRANDIDIER (1877) gibt in seiner Zusammenstellung aller von ihm veröffentlichten Haemophiliefälle für Tenna nur männliche und keine weiblichen Bluter an. Trotzdem er also das Vorkommen von weiblichen Blutern grundsätzlich bestätigt, findet er in den ihm von VIELI mitgeteilten allgemeinen Angaben und Krankengeschichten keine Veranlassung zur Annahme von weiblichen Haemophilen in Tenna.

Wenn dennoch VIELI (1846) die Bezeichnung «femme Bluter» verwendet und in seinem Bericht bei GRANDIDIER (1877) von «weiblichen Blutern» bzw. von «Bluterin» spricht, so ist es jeweils aus dem Text einwandfrei ersichtlich, daß er darunter nur die mit haemophiler Vererbung belasteten, also quasi an ihrer Konduktoreneigenschaft erkrankten Frauen versteht.

Im gleichen Sinne wird diese Bezeichnung von HOESSLI (1885) gebraucht, der ebenfalls das Vorkommen von weiblichen Haemophiliefällen in Tenna verneint:

«Ich bemerke hier aber noch ausdrücklich, daß ich keinen sichern Fall von haemophilen Blutungen bei einer Frau, wie sehr diese sonst auch den Charakter einer Bluterin gehabt haben mag, ausfindig machen konnte.»

Erst bei HOESSLY-HAERLE (1930) finden wir 8 Fälle von «weiblichen Blutern» (A VII. 9, A IX. 14, B VII. 178, B VII. 183, B IX. 331, B X. 450, C IX. 397 und C IX. 413), auch Frauen mit «Teilblutungen» bzw. mit «Blutungsneigung» benannt, die jedoch von HOESSLY-HAERLE in der Einleitung noch nicht als weibliche Haemophiliefälle angesehen werden:

«Ich schließe... meine Einleitung, mit der Feststellung, daß im Tennaer Stammbaum kein einziger Fall von echter Haemophilie beim Weibe während neun Generationen (d.h. die Zahl der von HOESSLY-HAERLE erfaßten Generationen, Verf.) vorkommt, was damit übereinstimmt, daß wir keine Frau auffinden konnten, die die Bedingungen der homozygoten Bluterin erfüllen würde, die also einer Bluterkonduktoreihe entstammt.

Hingegen fand ich acht Fälle von Frauen mit ‚Blutungsneigung‘.»

Die sehr ausführlichen Beschreibungen dieser «Teilbluterinnen» erwecken jedoch in einigen Fällen den Eindruck von echter weiblicher Haemo-

philie und sind sogar als solche in die Literatur eingegangen, wenn auch bereits an der Richtigkeit der Angaben gezweifelt wurde (MERSKEY, 1951b).

Eine sorgfältige Überprüfung aller dieser Fälle (siehe spezieller Teil dieser Arbeit) *gestattet uns nicht, sie als weibliche Haemophile zu betrachten und gibt auch keine Handhabe zur Aufstellung einer neuen nosologischen Einheit der «weiblichen Partialbluter».*

Von den 8 «Partialbluterinnen» lebten zur Zeit der Untersuchungen von HOESSLY-HAERLE (1930) nur deren 3 (B IX. 331, B. X. 450 und C. IX. 397). Sie gehörten oder gehören auch noch zu unseren Patienten bzw. deren engstem Verwandtenkreis. Die von B IX. 331 HOESSLY-HAERLE gegenüber angegebenen starken Blutungen bei Geburten von immerhin 8 Kindern genügen uns für die Diagnose der erhöhten Blutungsbereitschaft ebensowenig wie die nachweislich einmalige, wenn auch profuse Blutung nach Zahnextraktion von B X. 450 und das gelegentliche Vorkommen von Suffusionen bei C IX. 397; sorgfältige Nachforschungen ließen uns bei den 3 Frauen keine sonstigen Zeichen der Blutungsbereitschaft feststellen.

Von den übrigen 5 Fällen wird von HOESSLY-HAERLE bei B VII. 178 und B VII. 183 die Diagnose ihrer Blutungsbereitschaft ohne hinlängliche Begründung VIELI (bei GRANDIDIER, 1855a) zugeschrieben, trotzdem er, wie wir es dargelegt haben, die Blutungserscheinungen bei den Frauen von Tenna durchwegs bestreitet.

Bei den restlichen 3 Fällen müssen wir die von HOESSLY-HAERLE katamnestisch gestellte Diagnose der Blutungsneigung ebenfalls ablehnen, stützt sie sich doch bei A VII. 9 und A IX. 14 lediglich auf Verblutung bei der 5. resp. 6. Geburt und auf den bei den «rudimentären Blutern» bereits besprochenen «atypischen Erbgang». Bei C IX. 413 wird sie nur mit den nicht charakteristischen extramensuellen und Lungenblutungen ebenfalls ungenügend begründet.

Das klinische Krankheitsbild der Haemophilie scheint uns genügend scharf umrissen zu sein, um Ablehnung von Diagnosen zu gestatten, die anhand zufälliger Blutung ohne sonstiger haemophiler Symptome gestellt wurden. *Zu solchen nicht charakteristischen Blutungserscheinungen rechnen wir vor allem die weiblichen Genitalblutungen wie auch die Lungenblutungen bei beiden Geschlechtern und das Nasenbluten in der Jugend, wenn diese von keinen andern Zeichen der Blutungsbereitschaft begleitet sind.*

Im Falle von Tenna muß noch berücksichtigt werden, daß bis 1912 der nächste Arzt um eine Tagesreise entfernt gewesen ist und mangels baldiger ärztlicher Hilfe die atonischen Uterusblutungen, durch die vielen Geburten begünstigt, auch ohne haemophile Blutungsneigung relativ häufig vorkommen mußten.

Was die Erblichkeitsverhältnisse anbetrifft, *so ist im Stamme der Bluter von Tenna bis 1956 keine Bluter-Konduktorin-Kopulation nachweisbar und somit auch keine homozygote Konduktorin bekannt.*

Es besteht die Möglichkeit, daß die von VIELI (bei GRANDIDIER, 1877) und von HOESSLY-HAERLE (1930) beschriebenen häufigen Aborte und Menorrhagien bei den

Frauen aus dem Tenner Bluterstamm in Wirklichkeit durch Rhesus-incompatible Fehlgeburten bedingt gewesen sind (HUSER, 1953b). Unsere neuesten Kontrolluntersuchungen (IKIN, MOURANT, KOPEĆ, MOOR-JANKOWSKI und HUSER, 1957) haben die hohen Rh⁻-Häufigkeiten in Tenna und Umgebung erneut bestätigt.

Nach den hier angenommenen Richtlinien müssen wir auch die von PIANTA (1953) mitgeteilten Genital-, Magen- und Nasenblutungen einiger Konduktorinnen als von der haemophilen Anlage unabhängig ansehen. Die genaue Diskussion aller dieser Fälle bringen wir im speziellen Teil dieser Arbeit und beschränken uns hier lediglich auf eine kurze Zusammenfassung.

Bei folgenden Frauen wird die angebliche Blutungsneigung von PIANTA angenommen:

Konduktormutter	des Probanden 1	= B	IX. 331	
Konduktormutter	des Probanden 3	= B	X. 485	
Konduktormutter	des Probanden 4	= B	X. 497	
Konduktormutter	des Probanden 5	= C	X. 614	
Konduktormutter	der Probanden 6 und 7	= C	X. 601	
Konduktormutter	des Probanden 8	= C	X. 607	
Konduktormutter	des Probanden 9	= B	IX. 320	= Konduktorgroßmutter des Probanden 10
Konduktormutter	des Probanden 10	= B	X. 467	
Konduktorgroßmutter	der Probanden 1 und 2	= B	VIII. 256	= Konduktor-Urgroßmutter des Probanden 3
Konduktorgroßmutter	des Probanden 5	= C	IX. 397	
Konduktorgroßmutter	der Probanden 6, 7 und 8	= C	IX. 378	

Da weder die Bluter noch die Konduktorinnen in den Nachfahrentafelausschnitten von PIANTA numeriert sind, haben wir sie hier nach der laufenden Numerierung der Probanden in seinem Text beziffert, mit gleichzeitiger Angabe unserer entsprechenden Standortnummern. Wir korrigierten dabei die Verwechslungen der Mütter, Großmütter usw., die PIANTA unterlaufen sind.

Von seinen 11 «Konduktorinnen mit Blutungsbereitschaft» übernimmt PIANTA die 2 Fälle B IX. 331 und C IX. 397 von HOESSLY-HAERLE (1930); sie sind von uns bereits besprochen und ihre angebliche Blutungsbereitschaft widerlegt worden. Weitere 2 Fälle B VIII. 256 und C IX. 378 sind über 50 Jahre vor den Untersuchungen von PIANTA verstorben; sie lebten zur Zeit der Untersuchungen von VIELI (bei GRANDIDIER, 1855a und 1877) und von HOESSLI (1885), die, wie wir es bereits gezeigt haben, keinen Fall von Blutungsbereitschaft bei Frauen feststellen konnten. Auch unsere Nachforschungen, die fast gleichzeitig mit PIANTA durchgeführt wurden, gaben uns keine Handhabe, hier eine Blutungsneigung anzunehmen.

Dies ist ebenfalls bei B IX. 320 der Fall gewesen; ihr Tod an Ulkusblutung wird von PIANTA als Beweis ihrer Blutungsbereitschaft angesehen, trotzdem, wie er sagt, der haemophile Sohn «will nichts von Blutungen bei ihr wissen».

Desgleichen konnten wir im Laufe unserer Untersuchungen und langjährigen Beobachtungen keine Blutungserscheinungen bei den übrigen sechs heute noch lebenden Kon-

duktorinnen (B X. 485, B X. 497, C X. 614, C X. 601, C X. 607 und B X. 467) feststellen; auch unsere gerinnungsphysiologischen Untersuchungen (siehe dort) verliefen bei ihnen durchwegs negativ.

PIANTA, der bei den von ihm untersuchten Blutern auf die Gerinnungszeitbestimmungen verzichtete, führte sie bei den letzterwähnten 6 Konduktorinnen durch. Seine Angaben, mit welchen er die Blutungsbereitschaft bei den Frauen bestätigen will, sind aber derart unvollständig und widersprechend, daß wir sie hier zur Abklärung kurz besprechen möchten.

Die Gerinnungszeitbestimmungen wurden von PIANTA nach einer Methode von Prof. A. FONIO durchgeführt; ihre Technik wird in der Arbeit zwar kurz beschrieben, über die Messung und Bewertung der Ergebnisse heißt es aber lediglich (S. 163): «Nach dieser Methode beträgt der optimale (%, Verf.) Gerinnungszeitwert 30', Werte darüber sind als verlängert zu bezeichnen.» S. 195 wird aber auch der Wert von 30' als verlängert bezeichnet. Auch gibt der Autor weder Quellenangaben noch Zahlen an, auf Grund von welchen die von ihm als normal angesehene Gerinnungszeit berechnet wurde. Dazu sind noch seine Untersuchungsergebnisse – mit einer Ausnahme – jeweils mit zwei Werten angegeben: einer für «bewegt» (kürzer) und einer für «unbewegt» (länger), ohne den Bewertungsunterschied dieser 2 Werte auch nur zu erwähnen.

Der Autor selbst beurteilt seine Resultate keineswegs eindeutig. Bei keiner Konduktorin übersteigen die für «bewegt» angegebenen Werte 30'; für «unbewegt» dagegen findet PIANTA 45' bei B X. 497, 33' bei C X. 614 und 34' bei C X. 601. Nun werden aber auf S. 195 die 45' von B X. 497 und die 33' von C X. 614 als «etwas verlängerte Gerinnungszeit» angesehen, nicht aber die 34' von C X. 601, wobei aber die «bewegt» 25'/«unbewegt» 29' von B X. 467 an gleicher Stelle zu den «etwas verlängerten» Gerinnungszeiten berechnet werden. Schließlich wird in einer Zusammenstellung auf S. 196 lediglich die Gerinnungszeit von B X. 497 – diesmal für «unbewegt» mit 40' anstelle der früher (S. 171) angegebenen 45' – als «leicht verlängert» bezeichnet. Man erhält somit den Eindruck, daß der Autor selbst über die Bewertung seiner Untersuchungsergebnisse nicht im klaren gewesen ist: sie zur Bestätigung der angeblichen Blutungstendenz der Konduktorinnen zu benützen, ist selbstverständlich nicht angängig.

Wenn wir auch, wie bereits ausgeführt, den Gerinnungszeitmessungen ohne Faktorenfraktionierung nur wenig Bedeutung beimessen, so wollten wir sie doch bei PIANTA länger besprechen, da seine Beschreibung der angeblichen Blutungstendenz und Gerinnungszeitverlangsamung bei den Konduktorinnen auch durch FONIO (1954) übernommen wurde und bereits weitere Verbreitung (VOGEL, 1955a) gefunden hat.

Die Frage der «weiblichen Partialbluter», wie übrigens auch die der männlichen «rudimentären Bluter», wird abschließend am besten durch die Aussage von HOESSLI (1885) beleuchtet:

«Auch die vielen Fragen, die sich an die etwas dunkeln und unsichern Begriffe der latenten und rudimentären Haemophilie knüpfen, muß ich unbeantwortet lassen... Übrigens scheinen mir jene Fragen gar nicht so einfacher Natur zu sein, wie man so leicht anzunehmen geneigt ist, und glaube ich auch, daß *nur ein Hausarzt, der in der Lage ist, die Familien jahrelang genauer zu beobachten, zu einem zuverlässigen und sichern Urtheil gelangen kann* (kursiv von uns, Verf.). Es dürfte

aber noch lange dauern, bis ein Arzt in solche Beziehungen zu unsern Blutern kommt.»

In unserer Arbeit findet sich die von HOESSLI gestellte Voraussetzung das erste Mal erfüllt, nachdem G. TRUOG seit über 20 Jahren als Hausarzt den Großteil der lebenden Nachkommen (vgl. Tab. 5) des Tenner Bluterstammes betreut.

Die Ergebnisse der im Laufe von Jahren wiederholten klinischen Untersuchungen und Beobachtungen geben keinen Anlaß zur Annahme der Blutungsbereitschaft bei den Konduktorinnen aus dem Stamm von Tenna; die Resultate der gerinnungsphysiologischen Untersuchungen sprechen ebenfalls dagegen.

Wir mochten hier noch auf die mögliche Konduktorin C X. 629 (siehe spezieller Teil der Arbeit) hinweisen, bei welcher eine vor Jahren festgestellte Gerinnungszeitverlängerung von uns mit modernen Mitteln bestätigt werden konnte. Bei den normalen Faktor IX-Werten der Probandin kann jedoch, nach dem heutigen Wissen, kein Zusammenhang zwischen ihrer Gerinnungsstörung und der Haemophilie B in ihrer Familie gefunden werden.

4) Gerinnungsphysiologische Untersuchungen bei den Blutern, bei den sicheren und den möglichen Konduktorinnen und bei den gesunden Kontrollpersonen aus dem Bluterstamm von Tenna.

a. Theoretische Grundlagen

Seit den bahnbrechenden Arbeiten von WRIGHT (1893) und von SAHLI (1905), welche die Schwergerinnbarkeit des Blutes als die wesentliche Erscheinung des haemophilen Symptomenkomplexes bezeichnet haben, gehörte die Blutgerinnungsuntersuchung zu den wichtigsten Mitteln der Haemophiliediagnose. Von den verschiedenen Untersuchungsmethoden, wie z. B. die physikalischen und chemischen Untersuchungen des Gerinnens, hat sich in den letzten Jahrzehnten vor allem die Bestimmung der Gerinnungszeit eingebürgert (SCHLOESSMANN, 1930), trotzdem ihr von Anfang an die Unsicherheit der angewendeten Kriterien anhaftete. Um ein genaues Vorgehen zu ermöglichen und um die Fehlerquellen auszuschalten, wurden zahlreiche, oft recht komplizierte Methoden und Apparate vorgeschlagen (vgl. u. a. SCHLOESSMANN, 1930; ANDREASSEN, 1943), die wohl im einzelnen ein etwas genaueres Arbeiten gestatteten, aber deren Vielfalt sich nur ungünstig auswirkte, da sie den Vergleich der Untersuchungsergebnisse verschiedener Forscher verunmöglichte. Im übrigen bleibt es zwar unbestreitbar, daß bei den meisten Blutern Gerinnungsverzögerun-

gen in vitro mit verschiedenen Methoden festgestellt werden konnten: es sind jedoch seit den Untersuchungen von QUICK (1949) *mehrere sichere Haemophiliefälle mit normaler Gerinnungszeit* bekannt geworden, die von MERSKEY (1951a) zusammenfassend beschrieben wurden. In den letzten Jahren ist dann der Gerinnungszeitmessung als Test für die Koagulabilität des Blutes überhaupt nur ein relativer Wert beigemessen (WINTROBE, 1951) worden. Für die Differentialdiagnose der Haemophilie kann sie heute als irrelevant bezeichnet werden, da sie keinen Einblick in den Typus der haemophilen Erkrankung gestattet.

Im Gegensatz zu der früheren Auffassung wird die Haemophilie heute nicht mehr als eine nosologische Einheit angesehen, da die Fortschritte der Gerinnungsforschung in den letzten Jahren zu einer Differenzierung von wenigstens zwei sicheren haemophilen Gerinnungsstörungen geführt haben.

1911 zeigte ADDIS, daß eine geringe Menge von Globulinfraktion des normalen Plasmas die haemophile Gerinnungsstörung zu beheben vermag. Diese Beobachtung wurde später von GOVAERTS und GRATIA (1931), PATEK und STETSON (1936) und POHLE und TAYLOR (1937) bestätigt. 1946 wurde die im haemophilen Plasma fehlende Globulinfraktion von LEWIS, TAGNON, DAVIDSON, MINOT und TAYLOR beschrieben und antihaemophiles Globulin benannt. QUICK (1947) zeigte, daß diese Plasmaglobulinfraktion die Bildung von Thromboplastin aus Thrombocyten ermöglicht und bei Haemophilie defizient ist; er nannte sie Thromboplastinogen. KOLLER, KRÜSI und LUCHSINGER (1950) beschrieben eine Familie mit rezessiv geschlechtsgebundener haemorrhagischer Diathese, deren Glieder nur leichte klinische Erscheinungen, eine etwas verzögerte Blutgerinnung sowie einen wesentlich herabgesetzten Prothrombinverbrauch aufwiesen, ihr Plasma jedoch den Gerinnungsdefekt im Blut eines den Autoren bekannten Bluters aufhob. Die Verfasser nahmen an, daß es sich dabei um zwei pathogenetisch unterschiedliche Formen der Haemophilie handelt, die durch den Mangel an je einem verschiedenen Gerinnungsfaktor bedingt sind. Diese Vermutung ist dann von BIGGS et al. (1952), AGGELER et al. (1952) und SCHULMANN und SMITH (1952) mit verbesserter Technik bestätigt worden. BIGGS und DOUGLAS (1953) zeigten mit Hilfe des Thrombokinasestestes (Thromboplastin Generation Test), daß der eine Faktor während des Gerinnungsprozesses verschwindet, während der andere davon unberührt bleibt und auch im Serum nachweisbar ist.

Folgende Bezeichnungen sind für die beiden Faktoren vorgeschlagen worden (nach KOLLER, 1953a):

im Serum nicht oder kaum mehr feststellbar:

Gerinnungsfaktor VIII = antihämphiles Globulin

im Serum nachweisbar:

Gerinnungsfaktor IX = «Christmas» Factor

= PTC (Plasma Thromboplastin Component)

Die haemorrhagischen Diathesen, welche durch den Mangel dieser Faktoren verursacht werden, sind klinisch und genetisch nicht zu differenzieren. Bei den beiden können auch leichte, mittlere und schwere klinische Krankheitsbilder vorkommen.

Es ist nicht unsere Aufgabe, hier ein vollständiges Bild der neuen Erkenntnisse der Gerinnungsphysiologie zu geben. Auch wäre dazu eine längere Beschreibung in Form einer Diskussion nötig, da die divergierenden Meinungen der kompetenten Forscher noch keine als allgemein gültig anerkannte Synthese gestatten. Da sich jedoch im Zusammenhang mit dieser Meinungsverschiedenheit eine Vielfältigkeit der Nomenklatur ergeben hat, sahen wir uns gezwungen, als Einführung den Gang der neueren Untersuchungen zu erwähnen und im Folgenden eine kurze Zusammenstellung der gebräuchlichen Bezeichnungen anzugeben, wodurch die von uns des weiteren gebrauchten Begriffe genau festgelegt werden.

*Nomenklatur der haemophilen geschlechtsgebunden-rezessiven Gerinnungsstörungen
(jeweils der erste beschreibende Autor angegeben)*

Von uns angenommene Bezeichnung	Synonyma
Haemophilie A, CRAMER et al. (1953 a, 1953 b) KOLLER (1953 a, 1953 b). SOULIER u. LARRIEU (1953).	Klassische Haemophilie AHF (Antihemophilic Factor)-deficiency, AGGELER et al. (1952). Hemophilia, GRAHAM u. BRINKHOUS (1953). Hemophilia I, WIENER (1953). PTF (Plasma Thromboplastin Factor)-A deficiency, SPAET et al., zit. nach AGGELER et al. (1954). AHG (Antihemophilic Globulin)-deficiency, STEFANINI (1954).
Haemophilie B, CRAMER et al. (1953 a, 1953 b). KOLLER (1953 a, 1953 b). SOULIER u. LARRIEU (1953).	PTC (Plasma Thromboplastin Component)-deficiency, AGGELER et al. (1952). Christmas disease, BIGGS et al. (1952). Hemophiloid state C, GRAHAM u. BRINKHOUS (1953). Hemophilia II, WIENER (1953). PTF (Plasma Thromboplastin Factor)-B deficiency, SPAET et al., zit. nach AGGELER et al. (1954). Deuterohemophilia, AGGELER et al. (1954). Hemophilia-like state A, STEFANINI (1954).
Vollständigkeitshalber angegebene haemorrhagische Diathese mit autosomal- dominanter Vererbung (ROSENTHAL et al. 1955)	
PTA Plasma Thromboplastin Antecedent-deficiency, ROSENTHAL et al. (1953).	Hemophiloid state D, GRAHAM u. BRINKHOUS (1953). PTF (Plasma Thromboplastin Factor)-C deficiency, SPAET et al., zit. nach AGGELER et al. (1954). Hemophilia-like state B, STEFANINI (1954).

In unserer Arbeit gebrauchen wir die Terminologie von KOLLER, die eine allgemeine Verbreitung gefunden hat (vgl. auch TOCANTINS, 1954). Von den anderen gebräuchlichen Bezeichnungen scheint uns «Christmas» disease nicht gut angebracht zu sein, und die Abkürzung PTC müssen wir ablehnen als homonym mit der seit mehreren Jahren in der Humangenetik eingeführten Abkürzung für Phenyl-thiocarbamid (vgl. BOYD 1950, S. 278 ff.).

Für weitere Angaben über den Stand der heutigen Haemophilieforschung möchten wir auf den zusammenfassenden Bericht von VOGEL (1955c) verweisen. Originalbeiträge mit Stellungnahme der führenden Forscher sind im Symposium «What is Hemophilia» (AGGELER, WHITE und SPAET; MACFARLANE; QUICK; STEFANINI; TOCANTINS; KOLLER; PAVLOVSKY, 1954) zu finden. Einen Überblick über die neueste Literatur übermitteln die periodischen Literaturbesprechungen von KOLLER (1951, 1952, 1953b, 1953c, 1954b, 1955a, 1955b, 1956a, 1956b). Die moderne Darstellung der klinischen Seite der Gerinnungsprobleme ist bei DEUTSCH (1954) zu finden, der 1955 in einem zweiten Werk alle bis Mitte 1954 bekannten Gerinnungsfaktoren unter biochemischem Gesichtswinkel bearbeitet und mit einer sehr vollständigen Bibliographie versehen hat.

b. Technik und Ergebnisse der durchgeführten gerinnungsphysiologischen Untersuchungen

Die Blutuntersuchungen des Tenner Stammes wurden durch Dr. M. GEIGER im Gerinnungsphysiologischen Labor des Kantonsspitals Zürich (Prof. F. KOLLER) durchgeführt. Es wurde eine von GEIGER et al. (1955) angegebene Untersuchungsmethode, die im Folgenden kurz zusammengefaßt dargestellt wird, angewendet. Für eine ausführliche Beschreibung der Methodik verweisen wir auf die erwähnte Originalarbeit.

Die Blutproben wurden den Probanden an Ort und Stelle entnommen und zur Laboratoriumsuntersuchung nach Zürich gebracht.

Für die Serumuntersuchungen wurde vom Nativblut und für die Untersuchungen der Plasmafaktoren vom Oxalatblut ausgegangen. Das Serum wurde höchstens nach 12 Stunden, in einigen Fällen sogar 3 Stunden nach der Blutentnahme eingefroren.

Die untersuchten Probanden lassen sich in folgende Gruppen einteilen:

- (1) 10 Bluter
- (2) 4 Bluterbrüder = nichthaemophile Söhne sicherer Konduktorinnen
- (3) 11 sichere Konduktorinnen

- (4) 33 mögliche Konduktorinnen (jeweilige Wahrscheinlichkeit in ‰
für Vorhandensein des Haemophiliegens in Tafel 6 angegeben)
- (5) 8 Söhne der möglichen Konduktorinnen
- (6) 2 Söhne von Blutern

Die Kategorien (2) und (5) wurden untersucht, um unter ihnen die möglichen klinisch nicht manifesten Bluter (vgl. B XI. 507. im speziellen Teil der Arbeit) festzustellen; gleichzeitig ergaben sie zusammen mit (6) ein normales Vergleichsmaterial aus den Tenner Bluterfamilien.

Von allen untersuchten Tenner Probanden zeigten nur die Bluter pathologische Laboratoriumsbefunde (vgl. Fig. auf S. 47).

Die innerhalb einer biologischen Variationsbreite gleichlautenden Untersuchungsergebnisse der Probandengruppen gestatten die zusammenfassenden tabellarischen Darstellungen der Gesamtergebnisse, welche hier gebracht werden. Dadurch erübrigt sich eine separate Angabe der Laboratoriumsbefunde der einzelnen Probanden, so daß bei diesen im speziellen Teil der Arbeit lediglich das Untersuchungsdatum und das endgültige Ergebnis angegeben sind.

Untersuchungen im Serum

Prothrombinverbrauch, Einstufenmethode:

Normalwerte als Vergleich, gefunden ebenfalls bei (2), (5)

und (6)

1 ‰— 3‰

Untersuchte Tenner Bluter (1)

5 ‰— 30‰

Untersuchte weibliche Tenner Probanden (3) und (4)

1 ‰— 3‰

Faktor IX-Bestimmung, Einstufenmethode (vgl. GEIGER et al., 1955)

Prinzip: zu Oxalatplasma einer sehr schweren Haemophilie B werden 1:10 Verdünnungen der zu untersuchenden Sera zugegeben und nach Zugabe von Chloroform-Hirnextrakt die Rekalzitifizierungszeiten bei 37°C bestimmt.

Normalwerte als Vergleich, gefunden ebenfalls bei

(2), (5) und (6)

70 ‰—150‰

Bekannte Haemophilie B-Fälle als Vergleich:

leichte—mittlere

1 ‰— 15‰

schwere

unter 1 ‰

Untersuchte Tenner Bluter (1)

2,5‰— 6‰

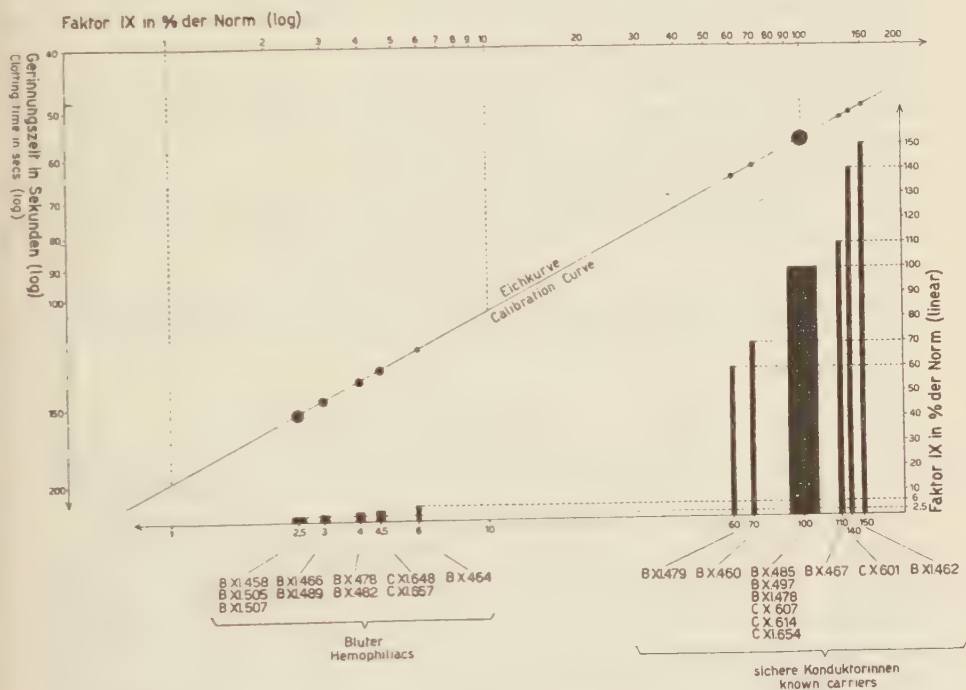
Untersuchte weibliche Tenner Probanden (3) und (4)

50 ‰—160‰

Pathologische Faktor IX-Werte können auch bei Thrombopenien und -pathien gefunden werden. Dies wurde aber für die Tenner Bluter ausgeschlossen, indem durch Zugabe von Hirn-Thrombokinasen zu Oxalatplasma und Rekalkifikation ein Serum erzeugt wurde, welches die Faktor IX-Werte unabhängig von der Thrombozytenzahl ergibt.

Fig. aus MOOR-JANKOWSKI, HUSER UND GEIGER (1957)

EINSTUFIGE FAKTOR IX - BESTIMMUNG BEI DEN BLUTERN UND KONDUKTORINNEN VON TENNA (Faktor IX = Christmas Factor = PTC)



ONE-STAGE DETERMINATION FAKTOR IX IN THE SERUM OF THE HEMOPHILIACS AND CARRIERS OF TENNA

Untersuchungen im Oxalatplasma

Rekalkifizierungszeiten

Normalwerte als Vergleich, gefunden ebenfalls bei

(2), (5) und (6)

Untersuchte Tenner Bluter (1)

Untersuchte weibliche Tenner Probanden (3) und (4)

80 Sek.–120 Sek.

160 Sek.–250 Sek.

80 Sek.–120 Sek.

Da bei den Probandinnen (3) und (4) und bei den untersuchten Nicht-blutern (2), (5) und (6) ein durchwegs normaler Prothrombinverbrauch und normale Rekalkifizierungszeiten gefunden wurden, konnte auf die nicht mehr relevante Thrombozytenzählung verzichtet werden.

Bei allen Bluterfällen wurden zusätzlich folgende Untersuchungen durchgeführt:

QUICK' Prothrombinkomplex, Faktor V, Faktor VII,
Prothrombin, Antithrombin und Fibrinogen.

Die gefundenen Werte liegen durchwegs im Normalbereich, so daß die haemorrhagische Diathese der Tenner Bluter auf ihre Störung nicht zurückgeführt werden kann. Es wurden auch jeweils die Bestimmungen des antihaemophilen Globulins = Faktor VIII, nach einer modifizierten Methode von BRINKHOUS (vgl. GEIGER et al., 1955) durchgeführt. Die gefundenen Werte fielen durchwegs normal aus, so daß das Vorkommen der Haemophilie A bei den Probanden ausgeschlossen ist.

Die detaillierte Aufstellung der durchgeführten Untersuchungen ist bei HUSER, MOOR-JANKOWSKI, TRUOG und GEIGER (1958) zu finden. Die zusammenfassende graphische Darstellung der Ergebnisse (s. S. 47) ist aus der Arbeit von MOOR-JANKOWSKI, HUSER und GEIGER (1957) entnommen.

B. Umfang der Erfassung von Blutern aus dem Bluterstamm von Tenna

1) Erfassung der zur Zeit der Bestandesaufnahme 1952–1956 lebenden Bluter.

Es kann angenommen werden, daß alle in den Jahren 1952–1956 lebenden Bluter aus dem Tenner Bluterstamm von uns als solche erfaßt worden sind. Bei der Bestandesaufnahme sind wir von unserer Nachfahren-tafel ausgegangen und haben *alle lebenden möglichen Träger des Haemophilie-gens* (vgl. Tafel 6) klinisch untersucht bzw. die Untersuchungsergebnisse der uns persönlich bekannten behandelnden Ärzte und Spitäler aufgenommen. In den allermeisten Fällen konnte ebenfalls eine gerinnungsphysiologische Untersuchung veranlaßt werden, u.a. auch zur Sicherung der Diagnose bei Kleinkindern, wo die klinischen Manifestationen des Leidens noch ausgeblieben sein könnten.

Nur bei folgenden Probanden konnte die Laboratoriumsuntersuchung nicht durchgeführt werden: B XI. 456, geb. 1942, in einem Alter, in welchem Haemophilie bereits klinisch manifest gewesen wäre (vgl. Alter bei der ersten Manifestation der Blutungsbereitschaft in Tab. 13), und bei den Brüdern C XII. 193, geb. 1951, und C XII. 194, geb. 1953, also beide

noch Kleinkinder, die uns jedoch aus täglichen Observationen bekannt sind und wo jedenfalls eine genaue klinische Untersuchung keine Anzeichen der Haemophilie feststellen ließ.

Von den 13 in den Jahren 1952–1956 lebenden *Blutern* konnten wir 11 persönlich klinisch untersuchen und die Untersuchungsergebnisse der uns bekannten Ärzte und Spitäler aufnehmen. Bei den 2 in den Vereinigten Staaten lebenden Blutern mußten wir uns mit den Mitteilungen aus dem nächsten Familienkreis begnügen. 10 Bluter konnten gerinnungsphysiologisch untersucht werden.

Das Erfassen aller Bluterfälle wurde uns durch die große Zahl der uns persönlich bekannten Nachkommen des Tenner Bluterstammes bedeutend erleichtert. Eine Übersicht darüber vermittelt die Tab. 5, in welcher nur unsere Patienten aufgeführt sind; die allermeisten davon aus der Praxis von G. TRUOG in der Zeit von 1934 bis 1956 und einige aus den sero-anthropologischen und genetischen Untersuchungen von H. J. HUSER und J. K. MOOR-JANKOWSKI 1952 bis 1955. Selbstverständlich lernt man aber bei Behandlung der Patienten, insbesondere in ländlicher Gegend, mit der Zeit

Tab. 5. Die als Patienten uns persönlich bekannten Nachkommen des Bluterstammes von Tenna, eingeteilt nach Generationen und Teilen der Nachfahrentafel. (Alle hier zusammengestellten Fälle sind im Namenverzeichnis mit P bezeichnet). (Siehe Bemerkung (2) und (3) zu Tab. 1, S. 7).

Descendants of Tenna Hemophiliacs Personally known as Patients to the Authors, grouped by generations and parts of Table of Descendants (all cases listed hereunder are markes P in the Register of Names). (See notes (2) und (3) concerning Tab. 1, p. 7).

Gene- rationen Gene- rations	Nachfahrentafel Teil A		Nachfahrentafel Teil B		Nachfahrentafel Teil C		Total Teile A, B und C		Total pro Gene- ration
	Part A of Table of Descendants		Part B of Table of Descendants		Part C of Table of Descendants		Total parts A, B and C		
	1956 am Leben alive in 1956	vor 1956 verstorben deceased before 1956	1956 am Leben alive in 1956	vor 1956 verstorben deceased before 1956	1956 am Leben alive in 1956	vor 1956 verstorben deceased before 1956	1956 am Leben alive in 1956	vor 1956 verstorben deceased before 1956	total per gene- ration
VIII.	—	6	—	4	—	—	—	10	10
IX.	22	26	33	44	6	10	61	80	141
X.	90	19	146	11	40	2	276	32	308
XI.	106	7	195	8	75	2	376	17	393
XII.	23	1	40	1	27	1	90	3	93
XIII.	—	—	—	—	—	—	—	—	—
					Gesamttotal		803	142	945

auch andere Familienmitglieder kennen, so daß der Kreis unserer persönlichen Beobachtungen noch weit über die in der Tab. 5 angegebenen Zahlen hinausreicht. Dazu kommen noch Angaben anderer behandelnder Ärzte, die uns während der 5 Jahre unserer Bestandesaufnahme mitgeteilt wurden; auch alle diese Ärzte hatten bei Behandlung der Patienten aus Bluterfamilien ein Interesse, dem Verwandtenkreis nachzuforschen, so daß sie uns jeweils Angaben über ganze Verwandtschaften mitteilen konnten.

Unter den geschilderten Umständen nehmen wir an, alle lebenden Bluter aus dem Tenner Bluterstamm erfaßt zu haben.

2) Erfassung der vor der Bestandesaufnahme 1952-1956 verstorbenen Bluter.

Die chronologisch erste Angabe über die Bluter von Tenna liefert das dortige Kirchenbuch, wo im Jahre 1741 der Verblutungstod des 1676 geborenen Samuel WALTHER (B III. 7) im Sterberegister verzeichnet ist.

Auch alle weiteren Angaben über die Bluter von Tenna sind bis 1784 lediglich aus dem Tenner Sterberegister zu entnehmen und werden erst von diesem Zeitpunkt an durch die Beschreibungen der behandelnden Ärzte und Vermerke im Kirchenbuch Versam vervollständigt (vgl. Tab. 13). In den anderen Ortschaften Graubündens, wo ebenfalls Bluter aus dem Stamm von Tenna aufgetreten sind (vgl. Fig. 1) konnten keine diesbezüglichen Vermerke in den Kirchenbüchern gefunden werden.

Die vollständige Aufnahme der Kirchenbücher von Tenna und von Versam ermöglichte uns, alle dort als Bluter bezeichneten Personen zu erfassen und sie in unserer Nachfahrentafel als solche zu bezeichnen.

Ob nun seit dem Beginn der erhaltenen Tenner Kirchenbücher um 1650¹⁾ bis zum Beginn der ärztlichen Beschreibungen in den achtziger Jahren des 18. Jahrh. noch andere Bluterfälle im Stamm von Tenna aufgetreten sind, ohne in den Kirchenbüchern erwähnt zu werden, bleibt ungewiß. Zusätzliche Angaben konnten weder im Archiv von Tenna noch in den Archiven und Kirchenbüchern der benachbarten Gemeinden gefunden werden. Immerhin gestattet uns auch das vorhandene Material einige Überlegungen zum Problem der Vollständigkeit unserer Erfassung von Blutern aus dem Stamm von Tenna in der Zeit um 1650 bis 1790.

Die in den Kirchenbüchern von Tenna und Versam aufgezeichneten Bluter sind als solche jeweils nur mit einer kurzen Randbemerkung bezeichnet; wir geben sie alle im speziellen Teil dieser Arbeit wortgetreu wieder. Mit einer Ausnahme (C VIII. 293) sind alle diese Aufzeichnungen

¹⁾ Die Sterberegister lassen Rückschlüsse bis um 1600 zu.

anlässlich des Verblutungstodes, als Bezeichnung der unmittelbaren Todesursache eingetragen. Es kann also mit einer gewissen Wahrscheinlichkeit angenommen werden, daß wenn es in Tenna vor dem Beginn der ärztlichen Beschreibungen um 1790 Bluter gegeben hätte, die nicht an offensichtlichem Verblutungstod gestorben sind, ihr Leiden in den Kirchenbüchern unerwähnt geblieben wäre. Immerhin mußte die Zahl der nicht an Verblutung Verstorbenen gering gewesen sein, was – in Anbetracht der vererbaren Erscheinungsform der Haemophilie (SCHLOESSMANN, 1930) – als Rückschluß aus der großen Häufigkeit des Verblutungstodes bei den späteren Generationen (vgl. Todesursachen in Tab. 13) gezogen werden kann.

Aber auch bei Fällen von offensichtlichem Verblutungstod besteht keine Gewähr, daß dieser im Sterberegister jeweils näher bezeichnet wurde, da die Todesursachen in den alten Kirchenbüchern nur ausnahmsweise vermerkt wurden. Als Beispiel mögen hier die 5 Verblutungsfälle dienen (B VI. 95, B VI. 96, B VI. 102, B VI. 105, C VII. 208), die alle in der Zeit 1790 bis 1809 in Tenna und Versam vorgekommen sind, jedoch in den Kirchenbüchern nicht erwähnt wurden und uns nur dank zeitgenössischen ärztlichen Berichten bekannt geworden sind.

Die Möglichkeit des Auftretens uns unbekannter Bluter aus dem Stamm von Tenna in der Zeit um 1650 bis 1790 ist also durch die Unvollständigkeit der vorhandenen Quellen gegeben. Die Zahl dieser möglichen Fälle ist aus der Nachfahrentafel des Tenner Bluterstammes ersichtlich. Die Wahrscheinlichkeit für das Auftreten des Haemophiliegens kann für jeden einzelnen Fall nach der von S. ROSIN entwickelten Methode (siehe S. 53 ff.) berechnet werden.

In der Tafel 2 sind alle diese möglichen Haemophiliefälle vor 1790, die uns als Bluter nicht bekannt sind, zusammengestellt. Wenn auch die für jeden einzelnen Fall in Prozent angegebenen Wahrscheinlichkeiten für das Auftreten des haemophilen Gens nicht ohne weiteres pro Generation addiert werden dürfen, so ist dennoch aus der Tafel die verhältnismäßig geringe Zahl der vor 1790 möglicherweise nicht erfaßten Haemophilen ersichtlich.

Die Möglichkeit, daß ein Bluter in der Nachfahrentafel als solcher nicht erfaßt wurde, ist nach 1790 gering und einige Jahrzehnte später fast ausgeschlossen, da sich seit Ende des 18. Jahrh. die Angaben aus den Kirchenbüchern von Tenna und von Versam mit den ärztlichen Beschreibungen von THORMANN (1837), VIELI (1846; bei GRANDIDIER, 1855a und 1877), HOESSLI (1885) und später von HOESSLY-HAERLE (1930) gegenseitig vervollständigen.

Tafel 2

ALLE THEORETISCH MOEGLICHEN HAEMOPHILIEFAELLE VOR 1790, DIE ALS
SOLCHE NICHT BEKANNT SIND AUSZUG AUS DER NACHFAHRENTAFEL DES BLUTERSTAMMES VON TENNA

Unter den Geschwisterschaften sind nur die theoretisch möglichen Haemophiliefälle samt ihrem Konduktoren-Elternteil und die für die Wahrscheinlichkeitsberechnung (siehe S 51) in Frage kommenden Personen nach Geburtsjahren geordnet angegeben

Dünn gezeichnet: lediglich zur Schilderung der Wahrscheinlichkeitsberechnung angegebene Fälle

- ☒ bekannter Haemophiliefall
- ☒ sichere Konduktorin
- ☐ mögliche Konduktorin
- ☐ mutmasslicher Haemophiliefall C V 74, siehe speziellen Teil der Arbeit

- ☒ Vollständigkeitshalber angegebene vor dem 6. Lebensjahr verstorbene männliche Kinder, die für die Wahrscheinlichkeitsberechnung nicht berücksichtigt wurden, da sie nicht mit Sicherheit als nicht-Häemophile bezeichnet werden können.

47	Standortnummer in der Nachfahrenstafel
1758	Im Jahr 1750 verstorbene, hier nicht aufgezeichnete Brüder
1761	Geburtsjahr
K.T.	Todesjahr, t = als Neugeborene gestorben
	Quellenangabe (vgl. nebenstehend)
<input type="checkbox"/>	theoretisch möglich, als solcher nicht bekannter Haemophiliefall vor 1790
50%	Wahrscheinlichkeit in % für das Vorhandensein des Haemophiliegens (siehe S. 51)

Abkürzungen der Quellenangaben

K. = Kirchenbuch
Z. = Zivilstandsregister
T. = Tenna
S. = Safien
Ve. = Versam
Val. = Valendas

ALL VIRTUALLY POSSIBLE CASES OF HEMOPHILIA BEFORE 1790, UNKNOWN AS SUCH, EXTRACT FROM DESCENDANTS TABLE OF HEMOPHILIACS OF TENNA

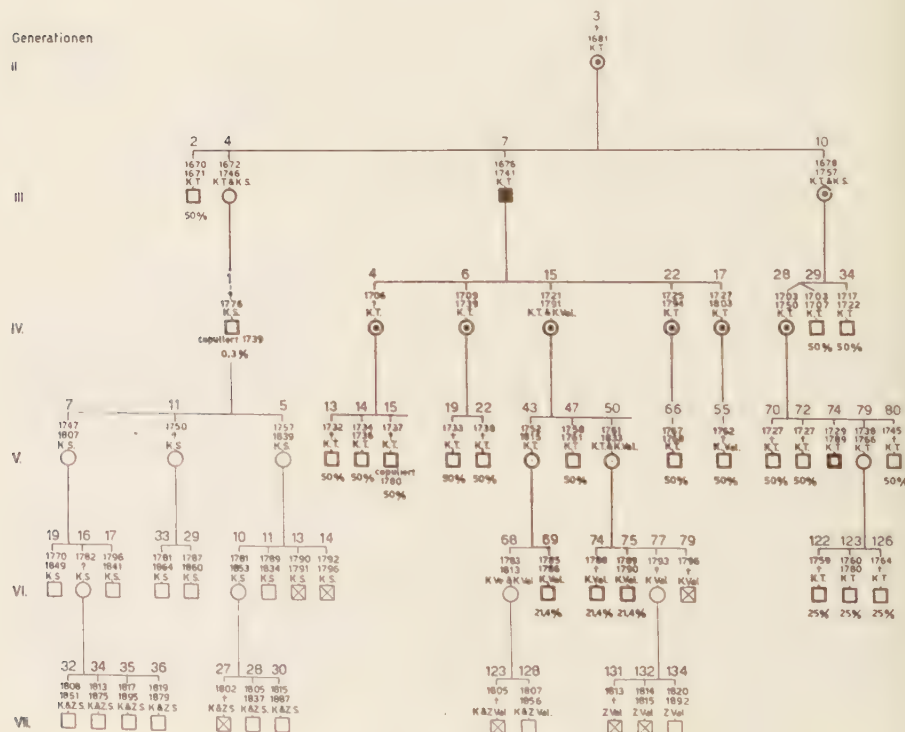
Thin printing: cases used for calculation of probabilities only

- | | | |
|---|------|--|
| Known case of hemophilia | 47 | Location number in descendants table |
| Known carrier | 1758 | Brothers deceased after 1750, not listed in this table |
| Possible carrier | 1761 | Year of birth |
| Presumptive hemophilic C.4.74,
see descriptive part of study | K.T. | Year of decease, + decreased before completion of 1st year of life
Source (cf. adjoining column) |
| | 50% | Virtually possible hemophilic, dived before 1750, unknown as such
Probability in % for presence of gene of hemophilia (see p. 51) |

☒ Male children dead before the completion of their 5th year of life. listed for the sake of completeness but not introduced into calculations of probabilities because of doubt in their non-hemophilic status.

Abbreviations for sources

M. = Perichial register	S. = Seiten
Z. = Register's list	Ve. = Versam
T. = Tenna	Vol. = Valendes



Anmerkung zur Legende: lies S. 53 statt S. 51

Es verbleibt nur noch die Frage, ob unter den nicht weiterverfolgbaren und nicht weiterverfolgten Nachfahren der Tenner Bluter (vgl. Tab. 4), bzw. unter deren Nachkommen, keine Haemophiliefälle aufgetreten sind. Für die wenigen unter ihnen, die als mögliche Träger des Haemophiliegens in Frage kämen, wurden die Wahrscheinlichkeiten in % für das Auftreten des Gens von S. ROSIN berechnet und in Tafel 1 angegeben. Wir nehmen jedoch an, daß ein solcher Bluter unseren Nachforschungen nicht entgangen wäre, wie wir dies für ähnliche Fälle im nachfolgenden Kapitel ausführlich begründen.

Zusammenfassend kann gesagt werden, daß es vor 1790 im Bluterstamm von Tenna einige Haemophile hätte geben können, die uns nicht als Bluter bekannt geworden sind; in den späteren Jahrzehnten ist diese Möglichkeit gering und seit um 1840 fast ausgeschlossen.

Bei allen diesen Überlegungen müssen selbstverständlich die als Kleinkinder vor einer wahrnehmbaren Manifestation des Leidens verstorbenen Träger des Haemophiliegens ausgeschlossen werden, wobei uns hier die oberste Altersgrenze von 6 Lebensjahren als angemessen erscheint (vgl. Alter bei der ersten Manifestation der Blutungsbereitschaft und Sterbealter beim Verblutungstod, Tab. 13).

Das Erfassen von haemophilen Kleinkindern noch vor den wahrnehmbaren Manifestationen der Haemophilie ist erst 1956 dank den gerinnungsphysiologischen Untersuchungen möglich geworden (vgl. B XI. 507 im speziellen Teil dieser Arbeit).

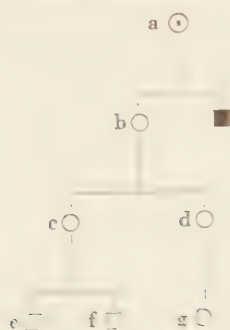
3) Berechnung der Wahrscheinlichkeiten für das Vorkommen des Haemophiliegens bei den Gliedern eines Bluterstammes,

von S. ROSIN.

Alle weiblichen Nachfahren der Bluter von Tenna haben die Möglichkeit, das Haemophiliegen von der Konduktorin II. 3 bekommen zu haben. Sie können also grundsätzlich Konduktorinnen sein. Die Wahrscheinlichkeit hierfür ist aber für die einzelnen Personen so sehr verschieden, daß es nötig ist, diese Größe für jede heute lebende Person zu berechnen. Es zeigt sich dabei, daß einige dieser grundsätzlich möglichen Konduktorinnen das Gen fast unmöglich erhalten haben können.

Die entsprechenden Wahrscheinlichkeiten ($=W$) werden wie folgt berechnet: Die W für die gegebene Stammbaumsituation unter der Annahme, die betreffende Person sei Konduktorin, wird dividiert durch die Summe der W aller phänotypisch gleichen Situationen.

An einem einfachen Beispiel soll dies näher erläutert werden:



a trägt das Gen mit Sicherheit, denn sie hat einen haemophilen Sohn.

e und f sollen mit Sicherheit ohne Haemophilie sein. Sie seien älter als 6 Jahre und ohne jegliche Anzeichen von Haemophilie.

Für die Frauen b, c, d und g ist zu berechnen, mit welchen W sie Konduktorinnen sind.

Berechnung für b:

Die Personen d und g leisten keinen Beitrag für die Frage, ob b das Gen hat oder nicht, weil sie keine männlichen Nachkommen haben, bei denen die Genwirkung hätte zum Vorschein kommen können. Dagegen ist e zu berücksichtigen, weil die gesunden Söhne e und f Rückschlüsse auf ihre Mutter c und ihre Großmutter b gestatten.

Wenn b das Gen haben soll, muß sie es (1) von a erhalten haben und (2) entweder gar nicht an c weitergegeben haben (2.1) oder dann ist es nach c gelangt, nicht aber nach e und f (2.2).

Die W für die Übertragung des Gens von einer Generation zur nächsten ist immer $= \frac{1}{2}$, weil die Konduktorinnen ja heterozygot sind. Ebenso groß ist die Wahrscheinlichkeit für die Nichtübertragung des Gens.

Die ganze Konstellation trifft zu, wenn sowohl (1) als auch (2) erfüllt ist: die W für (1) und (2) sind also zu multiplizieren. Die W für (2) setzt sich aber aus zwei Möglichkeiten zusammen, deren W zu addieren sind.

Die W der gegebenen Situation mit b als Konduktorin ist also folgende:

$$\frac{1}{2} \cdot \left(\frac{1}{2} + \frac{1}{2} \cdot \frac{1}{2} \cdot \frac{1}{2} \right) = \frac{5}{16}$$

(1) (2.1) (2.2)

Diese Größe ist aber auf die W der Gesamtheit aller denkbaren Stammbäume zu beziehen, die phänotypisch gleich sind wie der vorliegende; denn es ist ja schon bekannt, daß e und f das Gen nicht haben. Daher scheiden die Möglichkeiten mit e und f als Bluter zum vornherein aus.

Die im Stammbaum wiedergegebene Situation mit einer sicheren Konduktorin a und den beiden sicher gesunden Söhnen e, f in der 4. Generation entsteht mit folgender W:

Entweder erhält b das Gen nicht [$W = \frac{1}{2}$], dann ist es klar, daß es nicht auf e und f kommt; oder b bekommt das Gen, gibt es aber an c nicht

weiter $[W = (\frac{1}{2})^2]$ oder das Gen gelangt noch nach c zugleich aber nicht nach e und f $[W = (\frac{1}{2})^4]$.

Also wird die Gesamtwahrscheinlichkeit:

$$W = \frac{1}{2} + \frac{1}{4} + \frac{1}{16} = \frac{13}{16}$$

Die W für die uns interessierende Konstellation mit b als Genträger muss also dividiert werden durch $\frac{13}{16}$

$$W(b) = \frac{\frac{5}{16}}{\frac{13}{16}} = \frac{5}{13}$$

Für c ergibt sich nach der gleichen Methode:

$$W(c) = \frac{\frac{1}{16}}{\frac{13}{16}} = \frac{1}{13}$$

Dieses Ergebnis erhält man auch, wenn man b zunächst als Konduktorin betrachtet und die W für c dann mit $\frac{5}{13}$ multipliziert:

$$W(c) = \frac{5}{13} \left[\frac{\frac{1}{8}}{\frac{1}{2} + \frac{1}{8}} \right] = \frac{1}{13}$$

Die W für d muß die Hälfte von W (b) betragen und $W(g) = \frac{1}{4} W(b)$

$$W(d) = \frac{5}{26};$$

$$W(g) = \frac{5}{52}.$$

4) Können Bluter unter den Vorfahren bzw. unter den Geschwistern der Stamm-mutter des Tenner Bluterstammes und unter ihren Nachkommen vermutet werden?

Wie es bereits ausführlich besprochen wurde, war es uns nicht möglich, außer den Eltern (I. 1 und I. 2) des Stammvaters (II. 2) irgendwelche Vorfahren oder Geschwister des Stammelternpaares der Bluter von Tenna zu eruieren. Um dennoch die eventuellen Bluter des gleichen Stammes außerhalb unserer Nachfahrentafel, d.h. unter den Vorfahren oder auch unter den Geschwistern der Stammutter (II. 3) bzw. unter deren Nachkommen zu finden, haben wir nach Bluterstämmen oder einzelnen Blutern

gesucht, die in Zusammenhang mit dem Stamm von Tenna zu bringen wären. Unsere Nachforschungen sind ergebnislos verlaufen, trotz sorgfältiger Überprüfung des ganzen vorhandenen Archivmaterials von Tenna und Umgebung wie auch von Ortschaften, wo auf Grund von historischen Angaben oder Lokaltradition Beziehungen zum Tenner Bluterstamm vermutet werden konnten. Es gelang uns lediglich festzustellen, daß bei den Haemophiliefällen, die in der früheren Literatur (VIELI bei GRANDIDIER, 1855a und 1877; BULLOCH und FILDES, 1912) in Zusammenhang mit Tenna gebracht wurden, die gemeinsame Abstammung mit den Tenner Blutern sehr unwahrscheinlich ist.¹⁾ Es handelt sich dabei um die 3 haemophilen Brüder J. (siehe Tafel 4), die im speziellen Teil dieser Arbeit ausführlich besprochen werden, und um die von VIELI (bei GRANDIDIER, 1855a und 1877) beschriebenen Bluter von Rafna (wohl Roffna im Oberhalbstein) und von Reams, deren Abstammung von den Tenner Blutern von VIELI eigentlich nicht behauptet und bereits von HOESSLI (1885) überzeugend widerlegt wurde.

Der im speziellen Teil dieser Arbeit besprochene Bluter A IX. 10 scheint auf jeden Fall von keiner unbekannten Seitenlinie der Tenner Bluter abzustammen.

Im übrigen waren zur Zeit unserer Bestandesaufnahme noch folgende Bluterfälle in Graubünden bekannt (PIANTA, 1953): Stamm POOL-POOL von Soglio, Haemophilie erst vor 3 Generationen aufgetreten und in keine Verbindung mit den Blutern von Tenna zu bringen; ein Bluter in der Familie JEGEN-MALOIER in Landquart, mütterlicherseits aus Südtirol und Vorarlberg abstammend, und ein Bluter in der Familie HÖSSLI in Splügen, dessen Mutter aus dem Elsaß stammt; beide letzten Fälle ebenfalls ohne Verbindung mit dem Tenner Stammbaum.

Den einzigen Hinweis auf einen eventuell möglichen Zusammenhang eines Bluterstammes mit dem Stamm von Tenna fanden wir im Archiv des Kantonsspitals Glarus.²⁾ Die dort erhaltenen Angaben sind in Tafel 3 summarisch wiedergegeben. Es kann die Möglichkeit erwogen werden, ob die Stammutter der «Bluter im Sernftal», Verena BREHM, ursprünglich von Splügen, nicht gleicher Abstammung wie die Bluter von Tenna gewesen ist. Das Safiental und Tenna waren vor dem Bau der Talstraße 1880 in enger Verbindung mit Splügen über den Safierberg. Der dortige Saumweg war viel benutzt, da die Safier und Tenner Walser bei ihrer einseitigen Viehwirtschaft von jeher auf

¹⁾ Eine Ausnahme bildet hier der von CANTANI (1872) beschriebene Fall, den BULLOCH und FILDES (1912) mit den Tenner Blutern in Verbindung gebracht haben, ohne ihn jedoch dem Stammbaum eingliedern zu können. Es handelt sich hier um C VIII. 323, dessen Abstammung von C V. 74 HOESSLY-HAERLE (1930) eindeutig bewiesen hat.

²⁾ Wir sind Herrn Spitalarchivar H. RELLSTAB für seine hier wiedergegebenen Angaben verpflichtet.

Handelsverkehr mit Italien eingestellt waren (Joos, 1946) und sich auch als Säumer betätigten. Im übrigen ist Splügen auch eine Walsersiedlung, und Eheverbindungen zwischen den Walserkolonien waren häufig. Den Familiennamen BREHM treffen wir auch unter den alteingesessenen Safier und Tenner Geschlechtern. Damit sind aber auch die Hinweise auf mögliche gemeinsame Abstammung der Verena BREHM und der Tenner Bluter erschöpft. Verena BREHM mußte um 1600 geboren sein, da ihr 4. Sohn Hans 1630 geboren wurde. Das Taufregister von Splügen beginnt aber 1660 und das Ehe- und Sterberegister erst 1730, so daß dort nichts Näheres über die Familie zu finden ist. Auch das Archiv von Splügen enthält keine diesbezüglichen Angaben.¹⁾ Es konnte weder eine Familie BREHM aus Safien oder Tenna in Splügen, noch eine solche aus Splügen in Safien oder Tenna gefunden werden. Es kann somit ein Zusammenhang zwischen den Blutern von Tenna und den Blutern unter den Nachkommen von Verena BREHM nicht nachgewiesen werden. Sollte im übrigen der Ehemann von Verena MARTI, geb. 1655, (siehe Tafel 3) Bluter gewesen sein, was bei seiner Abstammung aus dem Bluterstamm ZWICKY möglich gewesen ist, so sind seine Nachkommen ebenfalls als Bluter aus diesem Stamm zu betrachten; es liegen jedoch keine Gründe vor, um eine gemeinsame Abstammung des Bluterstammes ZWICKY und desjenigen von Tenna anzunehmen.

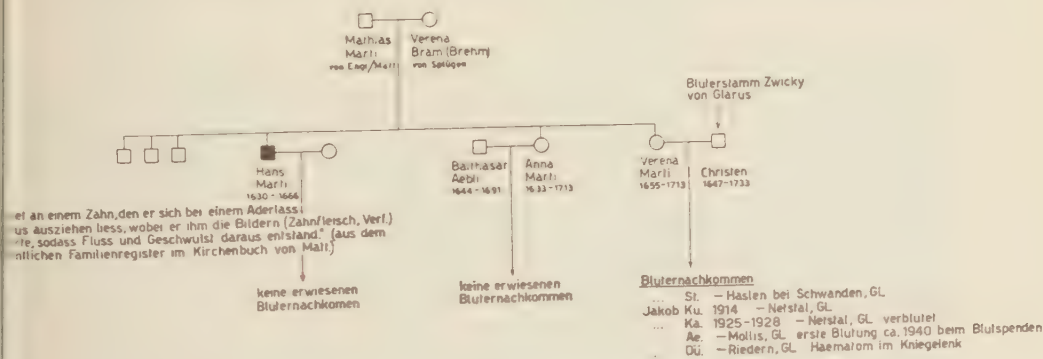
Die Angaben über Verena BREHM und ihre Nachkommen bringen wir hier nur vollständigshalber. Im Gegensatz zu unserem übrigen Material haben wir sie in den Originalquellen nicht nachgeprüft, da wir uns von den zeitraubenden Nachforschungen auf jeden Fall keine sichere Aussage über die Möglichkeit der gemeinsamen Abstammung mit den Tenner Blutern versprechen konnten. Eine solche wäre nur beim Vorhandensein der zeitgenössischen Kirchenbücher oder besonderer Archivquellen möglich gewesen.

Im Lichte der Ergebnisse unserer Nachforschungen kann das Vorkommen von uns unbekannten Seitenlinien der Bluter von Tenna bestritten werden.

Tafel 3

TER IM SERNFTAL, GLARUS, möglicherweise im Zusammenhang mit den Blutern von Tenna
haben vom Archiv der Kantonsbibliothek Glarus, H. RELLSTAB übernommen. Originalquellen nicht eingesehen

PHILIACS OF THE VALLEY OF SERNFT. Genealogical connections with Hemophiliacs of Tenna possible yet untraceable.
by H. RELLSTAB, Registrar of the Hospital of Glarus, original sources not seen by the authors.



¹⁾ Wir verdanken die Auskünfte Herrn Pfarrer P. HEINRICH, Splügen.

Mit der Ausnahme von A IX. 10 (siehe speziellen Teil der Arbeit) lassen sich alle früher und gegenwärtig bekannten Bluter in Tenna und Umgebung entweder auf das Stammelternpaar (II. 2 und II. 3) der Tenner Bluter zurückführen oder aber hängt ihre Abstammung mit großer Sicherheit nicht mit Tenna zusammen. Bei dem seßhaften Charakter der in Frage kommenden Bevölkerung von Tenna und Umgebung, die wir im Laufe unserer Nachforschungen etwa um 300 Jahre zurück erfassen konnten, wären uns eventuelle mit Haemophilie belastete Seitenlinien der Tenner Bluter schwerlich entgangen.

Für die Zeit vor etwa 1750 sind unsere Angaben, wie bereits ausgeführt, weniger genau, und was die etwaigen haemophilen Vorfahren des Stammelternpaares (II. 2 und II. 3) anbetrifft, so sind wir urkundenmäßig vollständig im ungewissen.

Als Hinweis auf das Alter und die Ausbreitung der Haemophilie in Tenna vor 1650 könnte immerhin eine lokale Legende bewertet werden, die bereits VIELI an GRANDIDIER (1855a) mitteilte. Danach soll auf den Blutergeschlechtern von Tenna ein Fluch lasten, seitdem einer ihrer Vorfahren als Richter einen Unschuldigen zum Tode verurteilt hat. Wir sind den Gegebenheiten, auf die sich die Legende bezieht, nachgegangen. Sie läßt sich in den Akten des Tenner Archivs auf eine Gerichtsverhandlung von 1779 zurückführen, wo der mutmaßliche Bluter Christian BÜHLER (C V. 74), Vorfahre zahlreicher Haemophiler, als Richter amtierte und den «Malefican» Hans Martin G., geb. 1732, (Kirchenbuch Tenna), wegen einiger Wilddiebstähle zum Tode verurteilte. Die 1769 erfolgte Hinrichtung durch Enthaupten ist im Gerichtsakt erwähnt, fehlt aber im Sterberegister des Kirchenbuches.

Der legendäre Fluch bezieht sich somit auf die Zeit nach der Gerichtsverhandlung und also auf die zahlreichen Bluterfälle, die vom Ende des 18. bis Mitte des 19. Jahrh. in Tenna unter den Nachkommen von Christian BÜHLER (C V. 74) und seiner Verwandten aufgetreten sind. Es ist verständlich, daß die häufigen Haemophiliefälle in der Nachkommenschaft einiger Familien der Dorfbevölkerung aufgefallen waren. Diesen war aber, wie wir es schon ausgeführt haben, der haemophile Erbgang in der 1. Hälfte des 19. Jahrh. bereits gut bekannt. Wenn trotzdem sein legendäres Entstehen auf die zur Zeit von VIELIs Berichten nicht weit zurückliegende Gerichtsverhandlung bezogen wurde, so kann angenommen werden, daß in den früheren Jahrhunderten die Haemophiliefälle in Tenna nicht gehäuft aufgetreten sind und deshalb von den Einwohnern nicht beachtet wurden. In diesem Falle wären der Bevölkerung erst die über 20 Bluterfälle aus dem Ende des 18. und Anfang des 19. Jahrh. aufgefallen, die auch das Erkennen des haemophilen Erbganges und der Krankheitssymptome gefordert haben. Damit wären aber auch die verhältnismäßig wenigen von uns erfaßten Bluter aus dem 17. und 18. Jahrh. als die ungefähre Gesamtzahl der zu jener Zeit aufgetretenen Bluter und somit auch das von uns angegebene Stammelternpaar (II. 2 und II. 3) als dasjenige der Tenner Bluter schlechthin zu betrachten.

Andererseits müssen auch irrationale Faktoren, die beim Entstehen einer Legende im Spiele sind, berücksichtigt werden. Diese haben sicherlich durch das *blutige* Todesurteil einen Auftrieb erhalten, besonders da es auf Grund einer dem damaligen Gerechtigkeits-

gefühl nicht mehr entsprechenden peinlichen Halsgerichtsordnung Karls V., wohl auf Wunsch des Feudalherren, gefällt wurde.

Zusammenfassend scheint es uns, den ganzen Bluterstamm von Tenna weitgehend vollständig erfaßt zu haben. Diese Annahme wird bekräftigt durch die erstellte annähernd lückenlose Nachfahrentafel des Stammelternpaares (II. 2 und II. 3) wie auch durch die negativen Ergebnisse unserer ausgedehnten Nachforschungen nach den haemophilen Seitenlinien. Im gleichen Sinne kann auch die Tenner Legende über die Vorfahren der Bluter ausgelegt werden.

5. Angaben über Fertilität und Sterblichkeit im Bluterstamm von Tenna und in einer Vergleichsbevölkerung

Bei der Aufstellung der Nachfahrentafel der Bluter von Tenna haben wir uns bemüht, ein möglichst vollständiges und einwandfreies Material für populationsgenetische Berechnungen, insbesondere für die Berechnung des Selektionsnachteiles der Tenner Bluter, zu erhalten.

Die Zusammenstellung in Form einer Nachfahrentafel, bei welcher nicht von einzelnen Probanden, sondern von einem nichthaemophilen Stammelternpaar ausgegangen wurde, gestattet alle erblichen Haemophiliefälle aus unserem Material in die Berechnungen einzubeziehen, ohne ihre Zahl durch eine Probandenkorrektur nach WEINBERG schmälern zu müssen.

Der Teil A der Nachfahrentafel stellt eine möglichst ideale *Vergleichsbevölkerung* dar, da sie nach Abstammung, Lebensweise, sozialer Stellung und Kulturkreis den beiden Bluter-Teilstämmen aus den Teilen B und C der Nachfahrentafel gleicht, ohne jedoch die haemophile Vererbung aufzuweisen.

Eine solche Vergleichsbevölkerung scheint uns den von ANDREASSEN (1943) als Vergleich zugezogenen nichthaemophilen Bluterbrüdern und ihren Familien überlegen zu sein. Denn es ist denkbar, daß die Familienverhältnisse eines Bluterbruders durch das Vorkommen der Haemophilie bei seinen Brüdern beeinflußt werden können, wodurch die Bluterbrüder und ihre Familien keine zufällige Stichprobe einer in gleichen Verhältnissen wie die Bluter lebenden nichthaemophilen Bevölkerung darstellen würden (ähnlich auch bei VOGEL, 1955a, S. 11). So könnte bei Unkenntnis des haemophilen Erbganges die Heiratsmöglichkeit eines Bluterbruders durch Angst vor haemophiler Vererbung verringert werden, desgleichen die Kinderzahl seiner einmal eingegangenen Ehe. Andererseits ist auch ein gegensätzliches Verhalten möglich, wenn ein Bluterbruder früher heiraten bzw. mehr Kinder zeugen würde, um die haemophilen Todesfälle oder die Todesbedrohung anderer Glieder seiner Familie auf diese Weise zu kompensieren, was z.B. bei einer Bauernbevölkerung denkbar ist, bei welcher die erbliche Hofübernahme bzw. Gutsbetrieb gemeinsam

mit eigenen Kindern in Frage kommen kann. In diesen beiden gegensätzlichen Fällen wäre aber die Kinderzahl der Bluterbrüder von der haemophilen Erkrankung ihrer Brüder nicht unabhängig und deshalb zum Vergleich ungeeignet.

Es muß auch mitberücksichtigt werden, daß im allgemeinen die Kinderzahl einer Person durch die Zahl ihrer eigenen Geschwister beeinflusst werden kann, und zwar durch Familientradition, affektive Einstellung, Erbschaftsaussichten u. a. m. Die Bluterbrüder stammen aber aus Geschwisterschaften, in welchen sich die Haemophilie manifestiert und möglicherweise die Größe dieser Geschwisterschaft beeinflußt hat (vgl. ROSIN, MOOR-JANKOWSKI, SCHNEEBERGER, 1958). Somit wäre aber wieder die Kinderzahl der Bluterbrüder von der haemophilen Vererbung in ihrer Familie nicht unabhängig.

Was hier über die mögliche Abhängigkeit der Kinderzahl der Bluterbrüder vom haemophilen Geschehen in der Familie gesagt wurde, gilt auch für die Kinderzahl der Schwestern von Blutermüttern.

Für die Berechnung des *Selektionsnachteiles* der Tenner Bluter sind die Angaben über die *Fertilität* in ihren Familien und über die *Sterblichkeit* der Bluter von Bedeutung.

Die *Fertilität* in den Bluterfamilien kann aus dem Vergleich der Kinderzahl in den Bluterfamilien mit derjenigen in der Vergleichsbevölkerung ermittelt werden.

Unter der Kinderzahl in den Bluterfamilien verstehen wir die *Kinderzahl der Bluter*, die in Tab. 6 gebracht wird, und die *Kinderzahl der Blutermütter*, die aus Tafel 5 (im Anhang) ersichtlich ist. Auf die Aufstellung einer Tabelle mit der Kinderzahl der Blutermütter haben wir verzichtet, da eine solche Zusammenstellung die Korrektur der Auslesefehler (vgl. ROSIN, MOOR-JANKOWSKI, SCHNEEBERGER, 1958) nicht gestattet und somit für Vergleichszwecke unbenützbar sein würde.

Das Vergleichsmaterial zur Kinderzahl der Bluter bringen wir in Tab. 8, dasjenige zur Kinderzahl der Blutermütter in Tab. 10 und 11. Vollständigkeitshalber wird auch die Kinderzahl der Bluterbrüder (Tab. 7) und diejenige der Schwestern von Blutermüttern (Tab. 9) angegeben, wobei wir aber, wie bereits gesagt, diese Zahlen nicht als gültiges Vergleichsmaterial ansehen.

Zur Vereinfachung der Berechnungen wurden die Tabellen 6 bis 11 generationsweise zusammengestellt, was nur eine gröbere zeitliche Einteilung erlaubt. Als Anhaltspunkt für die zeitliche Orientierung in der Generationenfolge wurde die Einteilung in die Zeitperioden vor und nach etwa 1800 eingeführt.

In diesem Zusammenhang muß erwähnt werden, daß sich die Lebensverhältnisse für den Großteil der in Graubünden lebenden Bluter und der Vergleichsbevölkerung seit dem 17. Jahrh. nicht sehr stark geändert haben und bis in die Zeit 1880 bis 1910, also bis und mit der IX. Generation, sind jedenfalls kaum irgendwelche Änderungen anzunehmen.

Tab. 6. Bluter und ihre Kinder — Hemophiliacs and their Children

	Generation der Bluter Generation of hemophiliacs	verheiratet married		ledig un- married	E —	Generation der Kinder Generation of children	Kinderzahl (Geschwisterschaften) Number of children (siblings)											
		mit Kindern with children	ohne Kinder without children				to- tal	1	2	3	4	5	6	7	8	9	10	11
vor etwa 1800 before about 1800	III IV V VI	1 1 1 1	- - - 1	- 2 - 5	- - - -	IV V VI VII	11 2 5 3	- 1 - -	- - - 1	- - - -	- - 1 -	- - - -	- - 1 -	- - - -	- - - -	- - - -		
nach etwa 1800	VII VIII IX Xa geboren vor 1901 born before 1901	5 2 2 1	- - - -	4 7 4 3	- 1 - -	VIII IX X XIa	22 9 5 1	2 - 1 1	- - - -	- 1 - -	- 1 - -	- - 1 -	- - - -	2 1 - -	- - - -	- - - -		
after about 1800	Xb geboren nach 1901 born after 1901 XI XII	3 1 -	- - -	- 9 1	- - -	XIb XII	9 2	- -	1 1	1 -	- -	- -	- -	- -	- -	- -		
total vor etwa 1800 total before about 1800		4	1	7	-	total vor etwa 1800 total before about 1800	21	-	1	1	-	-	1	-	-	-		
total nach etwa 1800 ohne Generation Xb-XII total after about 1800 without Generation Xb-XII		10	-	18	1	total nach etwa 1800 ohne Generation Xb-XII total after about 1800 without Generation Xb-XII	37	4	-	1	1	-	3	-	1	-		
Gesamttotal ohne Generation Xb-XII total without Generation Xb-XII		14	1	25	1	Gesamttotal ohne Generation Xb-XII total without Generation Xb-XII	58	4	1	2	1	1	3	-	1	-		

Tab. 7. Kinderzahl der Bluterbrüder
Number of Children of Brothers of Hemophiliacs

Zeitspanne Period of time	Kinderzahl (Geschwisterschaften) Number of children (sibships)							
	0	1	2	3	4	5	6	7
vor 1800 before 1800			—	—	—	—	—	—
nach 1800 after 1800	1	3	1	1	2	2	—	1

In Tab. 6, 8, 10 und 11 sind je nach den in dem dargestellten Material vorkommenden Personenkategorien folgende Kolonnen nur vollständigkeitshalber eingeführt worden: ? = nicht weiterverfolgbar, ? = nicht weiterverfolgt, E = emigriert und nicht weiterverfolgbar (vgl. S. 25). Die in diesen Kolonnen aufgeführten Personen können für die Berechnung der durchschnittlichen Kinderzahl nicht verwendet werden.

In Tab. 6 haben wir die X. Generation der Bluter in die vor und nach 1901 geborenen eingeteilt. Diese Einteilung hat sich infolge der Generationenverschiebung zwischen dem Teil B und C der Nachfahrentafel (vgl. Tafel 5) als nötig erwiesen. Sie gestattete uns, die vor 1901 geborenen Bluter aus dem Teil C der Nachfahrentafel als Generation Xa zu erfassen. Da die in dieser Generation Xa erfaßten 4 Bluter vor 15 bis 57 Jahren verstorben sind und somit ihre Kinderzahl vollständig erfaßt ist, können sie für die Berechnung der Bluterfertilität mitverwendet werden, im Gegensatz zu den 3 Blutern aus der Generation Xb, deren Ehen noch im Fortpflanzungsalter stehen (Ehefrau nach 1906 geboren).

Um ein übereinstimmendes Vergleichsmaterial zu erhalten, mußte auch in der Tab. 8 die Generation X entsprechend in Xa und Xb geteilt werden.

Das Vergleichsmaterial in Tab. 8 besteht aus den männlichen *Nachkommen* aus dem Teil A der Nachfahrentafel und ihren Kindern. Die angeheirateten Männer sind nicht mitberechnet, weil wir ihre Brüder, die z.B. im Kindesalter verstorben oder aber ledig geblieben sind, nicht erfassen können, so daß durch das Berechnen der lediglich in unserer Nachfahrentafel angeheirateten Männer ein Auslesefehler entstünde, welcher die durchschnittliche Kinderzahl künstlich erhöhen würde.

Um komplizierte Zählungen zu vermeiden, wurden von den männlichen Nachkommen im Teil A der Nachfahrentafel nur diejenigen für die Tab. 8

Tab. 8. Männliche Nachkommen aus Teil A der Nachfahrentafel und ihre Kinder
Male Descendants from Part A of Table of Descendants and their Children

	Generation der Väter Generation of fathers	verheiratet married		ledig un-married	?	?	E	Tot-geburth still-birth	Generation der Kinder Generation of children	Kinderzahl (Geschwisterschaften) Number of children (siblings)								
		mit Kindern with children	ohne Kinder without children							to- tal	1	2	3	4	5	6	7	8
vor etwa 1800 before about 1800	IV	1	-	-	-	-	-	-	V	6	-	-	-	-	-	-	-	-
	V	2	-	1	-	-	-	-	VI	10	-	-	-	-	2	-	-	-
	VI	6	1	2	1	-	-	-	VII	24	-	1	1	2	1	1	-	-
nach etwa 1800 after about 1800	VII	13	3	11	1	-	-	-	VIII	46	1	5	1	1	4	-	-	1
	VIII	11	1	13	2	-	5	-	IX	37	1	3	3	2	-	1	1	-
	IX	13	5	14	-	-	12	-	X	45	1	2	4	4	1	-	1	-
	X ^a	5	1	6	-	-	-	-	XI ^a	18	1	1	1	1	-	-	-	1
	geboren vor 1901 born before 1901																	
total vor etwa 1800 total before about 1800	X ^b	23	-	21	-	-	-	-	XI ^b	68	3	8	5	4	-	3	-	-
	geboren nach 1901 born after 1901																	
	XI	6	1	75	-	1	-	1	XII	17	-	3	1	2	-	-	-	-
total nach etwa 1800 total after about 1800		9	1	3	1	-	-	-	total vor etwa 1800 total before about 1800	40	-	1	1	2	3	2	-	-
	total nach etwa 1800 ohne Generation Xb-XI	42	10	44	3	-	17	-	total nach etwa 1800 ohne Generation Xb-XI	146	4	11	9	8	5	1	2	2
	total after about 1800 without Generation Xb-XI								total after about 1800 without Generation Xb-XI									
Gesamttotal ohne Generation Xb-XI		51	11	47	4	17	-	-	Gesamttotal ohne Generation Xb-XI	186	4	12	10	10	8	3	2	2
	total without Generation Xb-XI								total without Generation Xb-XI									

Familie des sporadischen Bluters A IX. 10 nicht aufgeführt
Members of the family of the sporadic hemophilic A IX. 10 not listed.

Tab. 9. Kinderzahl der Schwestern von Blutermüttern
Children of Sisters of Mothers of Hemophiliacs

Generation, in der die Kinder berechnet sind Generation in which the children are listed	Kinderzahl (Geschwisterschaften) Number of children (sibships)												
	0	1	2	3	4	5	6	7	8	9	10	11	12
IV. (um 1710) (about 1710)	-	1	-	-	-	-	-	-	-	-	-	-	-
V. (um 1740) bis Jahr 1800 (about 1740) until 1800	-	-	-	-	-	-	-	-	-	-	-	-	-
total vor 1800 total before 1800	-	1	-	-	-	-	-	-	-	-	-	-	-
total nach 1800 total after 1800	2	-	5	7	4	-	1	-	-	-	-	-	1
Gesamttotal	2	1	5	7	4	-	1	-	-	-	-	-	1

zusammengezählt, die direkt im Teil A zu finden sind, nicht aber die Nachkommen, die durch Verweise in den Teilen B und C aufzufinden wären.

Der sporadische Bluter A IX. 10 und seine 3 Brüder wurden im Vergleichsmaterial nicht mitberechnet, sein Vater A VIII. 8 wurde lediglich als Kind seines Vaters A VII. 8 gezählt.

Für die Beurteilung der relativ großen Kinderzahl der Blutermütter, die aus Tafel 5 (im Anhang) ersichtlich ist, muß berücksichtigt werden, daß den Tenner Bluterfamilien die Vererbung der Haemophilie durch Konduktorinnen, und zwar nur auf einen Teil der Söhne, bereits am Anfang des 19. Jahrh. bekannt gewesen ist (vgl. S. 35 und 37). Es ist nun denkbar, daß in den Ehen der Blutermütter mehr Kinder gezeugt wurden, um der Gefahr des frühzeitigen Verlustes aller männlichen Nachkommen an Haemophilie vorzubeugen. Die Kinderfreudigkeit bei einer vorwiegend bäuerlichen Bevölkerung hat hier sicherlich auch eine Rolle gespielt.

Das Vergleichsmaterial zur Kinderzahl der Blutermütter (aus Tafel 5 im Anhang) ist in Tab. 10 und 11 zusammengestellt.

Für Tab. 10 wurden ähnlich wie für Tab. 8 nur die im Teil A der Nachfahrentafel auftretenden weiblichen Nachkommen zusammengezählt, nicht aber die Nachkommen, die durch Verweise in den Teilen B und C aufzufinden wären.

Tab. 10. Weibliche Nachkommen aus Teil A der Nachfahrentafel und ihre Kinder
Female Descendants from Part A of Table of Descendants and their Children

	Generation der Mütter Generation of mothers	verheiratet married		ledig un- married	?	?	E	Generation der Kinder Generation of Children	Kinderzahl (Geschwisterschaften) Number of children (siblings)								
		mit Kindern with children	ohne Kinder without children						to- tal	1	2	3	4	5	6	7	8
vor etwa 1800 before about 1800	V	3		3	2			VI	11		1	2					
	VI	6						VII	28	1	1		1	1	2		
nach etwa 1800 after about 1800	VII	11	3	6	3	1		VIII	38	2	3		2	2	2		
	VIII	17	3	13	1	6	5	IX	48	2	10	1	1	1	1		1
	IX	22	1	10		3		X	80	1	5	6	5	2	1	1	1
	Xa geboren vor 1916 born before 1916	23	6	12		1		XIa	82	3	2	5	8	4			1 ¹
	Xb geboren nach 1916 born after 1916	1		8		3		XIb	1		1						
total vor etwa 1800 total before about 1800		9		3	2			total vor etwa 1800 total before about 1800	39	1	1	1	2	1	1	2	
total nach etwa 1800 ohne Generation Xb								total nach etwa 1800 ohne Generation Xb									
total after about 1800 without Generation Xb		73	13	41	4	8	8	total after about 1800 without Generation Xb	248	8	20	12	16	9	4	1	3
Gesamttotal ohne Generation Xb Total without Generation Xb		82	13	44	6	8	8	Gesamttotal ohne Generation Xb Total without Generation Xb	287	9	21	13	18	10	5	3	3

1) davon 1 Totgeburt
1 still-birth included

Tab. 11. Frauen aus den Bluterfamilien in Teil B und C der Nachfahrentafel und ihre Kinder
 Females of the Hemophilic Families in Parts B and C of Table of Descendants and their Children

Generation der mütterlichen Geschwertschaft Generation of the mothers' sibships	verheiratet married	ledig un- married	Gen- eration der Kinder Generation of children	Kinderzahl (Geschwertschaften) Number of children (sibships)										
				Tot- tal										13
				1	2	3	4	5	6	7	8	9	10	
vor etwa 1800	III	1	IV	11	1									1
	IV	2	V	34		1	2	2	1					
	V	1	VI	5				1						
	VI	1	VII	19	1	1	2	1	1					
		5	VII	29	2	1	1	1	1					
		7		2	1									
		1												
		13		63	13	2	3	2	1	2	1	1		
nach etwa 1800 after about 1800	VII	3	VIII	7	1	2								
	VIII	11	IX	49	1	4	1	1	2	1				1
	IX	1	X	11	1			1	2					
	X ^a	3	XI ^a	38	1	1	1	1	2					1
	X ^b	7		12				1	1					
		2		9	1	1	1							
		3												
		5		17	1	1	3							
	XI	4	XII	13		3	1							
		5		13	1	1	2	1						
	XII													

1) X^a - ledig, nicht hemophilic father or brothers 2) X^b - Females without hemophilic father or brothers 3) Totgeburt,

Standortnummern der in Tab. 11 aufgeführten Frauen

Location Numbers of Females listed in Table 11

III.		4	10	11														
IV.	B	4	6	15	17	20	22											
	C	23	28	31	32	33												
V.	B	52	53	54	56	58	60	62	63	65								
	C	71	76	77	79													
VI.	B	89	94	101	104													
	C	114	116	118	121													
VII.	B	138	139	153	155	162	165	170	172	174	178	179	181	183				
	C	190	194	204	205	210	212											
VIII.	B	144	204	219	221	246	247	249	251	252	254	255	256	267	271	275	276	278
	C	292	295	298	304	305	307	310	312	313	314	316	318	348	353	355		
IX.	B	266	269	273	318	320	322	326	327	331	333							
	C	378	383	384	387	388	389	394	395	397	408	413						
X.a	B	444	446	447	448	449	450	451	454	463	468							
	C	598	601	602	607	610	612	614	626a	629								
X.b	B	456	460	467	473	481	485	490	493	497								
	C																	
XI.	B	457	462	463	464	465	471	478	479	506								
	C	643	646	651	652	654	656	659	660	671	673							
XII.	B																	
	C	184	186															

In den beiden Tabellen 10 und 11 wurde in Anlehnung an die Darstellung in den Tabellen 6 und 8 die Generation X in Xa und Xb eingeteilt. Die Generation Xa erfaßt Frauen, deren Fortpflanzungsperiode bei unserer Bestandesaufnahme im Jahre 1956 abgeschlossen war und die deshalb für die Fertilitätsberechnungen mitverwendet werden können. Die Frauen aus der Generation Xb standen in der Zeit unserer Bestandesaufnahme noch im Fortpflanzungsalter, dessen Abschluß mit dem fünfzigsten Lebensjahr angenommen wurde. In Tab. 11 wird das vierzigste Lebensjahr als Ende der Fortpflanzungsperiode bei *ledigen* Frauen angesetzt, da ältere Erstgebärende in dem Beobachtungsgut praktisch nicht vorkommen. Diese genaue Einteilung wurde in Hinsicht auf möglichst vollständiges Erfassen des ganzen gesammelten Materials durchgeführt.

Um den hier bereits erwähnten möglichen Einfluß des haemophilen Geschehens auf die Kinderzahl im engen Verwandtschaftskreis zu eruieren, wurden die in Tab. 11 erfaßten Frauen in solche mit und solche ohne Bluter-väter oder Bluterbrüder eingeteilt.

Für die Auswertung des hier gebrachten Materials und für weitere detaillierte Angaben über die Fertilität im Bluterstamm von Tenna wird auf die Arbeit von ROSIN et al. (1958) verwiesen. Im übrigen können anhand unserer Nachfahrentafel und des Namenverzeichnisses (siehe S. 78 ff.) alle erwünschten Berechnungen durchgeführt und unsere tabellarischen Angaben überprüft werden.

Die Angaben über die Sterblichkeit im Bluterstamm von Tenna werden durch Tab. 12 und Fig. 2 und 3 sowie durch die Übersicht in Tab. 13 vermittelt.

In Tab. 12 wird zusätzlich zu unserem Material eine tabellarische Zusammenstellung aus dem Material von SCHLOESSMANN (1930) gebracht, welche zur Veranschaulichung der Verblutungssterblichkeit in anderen Bluterstämmen dienen soll. Bei Vergleich unserer Angaben mit denjenigen von SCHLOESSMANN muß berücksichtigt werden, daß sein Material aus verschiedenen Bluterstämmen und ohne die damals unbekannte, gerinnungsphysiologische Differenzierung der Haemophilie zusammengestellt wurde, also inhomogen ist.

Auffallend gegenüber den Tenner Blutern ist im Material von SCHLOESSMANN die hohe Zahl der Verblutungsfälle im Pubertätsalter, wie sie übrigens auch von ANDREASSEN (1943, S. 34) in seinem großen, ebenfalls inhomogenen Material gefunden wurde. Wenn auch der Verblutungstod an sich wenig über die Schwere der haemophilen Erkrankung aussagt, so lange nicht wenigstens auch das auslösende Trauma bekannt ist, so kann die Häufung der jugendlichen Verblutungsfälle innerhalb eines Beobachtungs-

Tab. 12. Sterbealter der am Verblutungstod verstorbenen Bluter
Duration of Life of Hemophiliacs Dead of Bleeding

	Sterbealter Duration of Life							Total
	1-9 Jahre	10-19 Jahre	20-29 Jahre	30-39 Jahre	40-49 Jahre	50-59 Jahre	60-69 Jahre	
Bluter von Tenna ¹⁾ Hemophiliacs of Tenna ¹⁾	12	2	6	4	1	3	1	29
	1-10 Jahre	10-20 Jahre	20-30 Jahre	30-40 Jahre	40-50 Jahre	50-60 Jahre	60-70 Jahre	Total
Material von SCHLOESSMANN (1930, S. 73)	18	13	8	4	—	2	1	46

¹⁾ ohne A IX. 10.
without A IX. 10.

gutes, das wie bei SCHLOESSMANN und ANDREASSEN größtenteils aus Familien mit mehreren Blutern besteht, doch als Hinweis auf eine vorwiegend schwere Form der Erkrankung im betreffenden Beobachtungsgut gedeutet werden. Somit kann das Material von SCHLOESSMANN und dasjenige von ANDREASSEN nur zum kleinen Teil aus Bluterstämmen bestehen, welche die gleiche Erscheinungsform der Haemophilie wie der Tenner Stamm aufweisen, da sonst die Verblutungsrate im Pubertätsalter nicht so hoch sein könnte. Diese Überlegung gibt uns einen Hinweis auf die nicht starke Verbreitung der Tenner Erscheinungsform der Haemophilie, die z. B. in einem für ein ganzes Land (Dänemark) repräsentativen Material von ANDREASSEN nur wenig vertreten zu sein scheint.

In der gleichen Richtung wie der Unterschied in der Pubertätssterblichkeit geht auch der Unterschied zwischen dem mittleren Sterbealter im Tenner Bluterstamm und im Material von ANDREASSEN. ANDREASSEN gibt das mittlere Sterbealter seiner 105 Bluter als $16\frac{1}{2}$ Jahre an, wobei er eine Korrektur durch Wegnahme der 16 bis 17 Jahre vor seiner Bestandesaufnahme Verstorbenen vorschlägt, wodurch das mittlere Sterbealter auf 18 Jahre erhöht wird. Das mittlere Sterbealter der Bluter aus dem Stamm von Tenna kann aus Tab. 13 berechnet werden, wobei der sporadische Fall A IX. 10 und die 2 Fälle mit unbekanntem Todesdatum C VII. 197 und B VIII. 265 nicht mitzuzählen sind. Eine zusätzliche Korrektur wird von uns als unnötig erachtet, so daß sich für die 40 verstorbenen Tenner Bluter ein mittleres Sterbealter von 27,7 Jahren ergibt, das also bedeutend über demjenigen für das dänische Blutermaterial liegt.

Bei 28 von den 40 verstorbenen Tenner Blutern ist uns die Verblutung als Todesursache bekannt; das mittlere Sterbealter der Verbluteten (vgl. Tab. 12 und 13) beträgt 23,4 Jahre.

Der Vergleich der Sterblichkeit in den Tenner Bluterfamilien und in einer Kontrollbevölkerung soll durch Fig. 2 veranschaulicht werden.

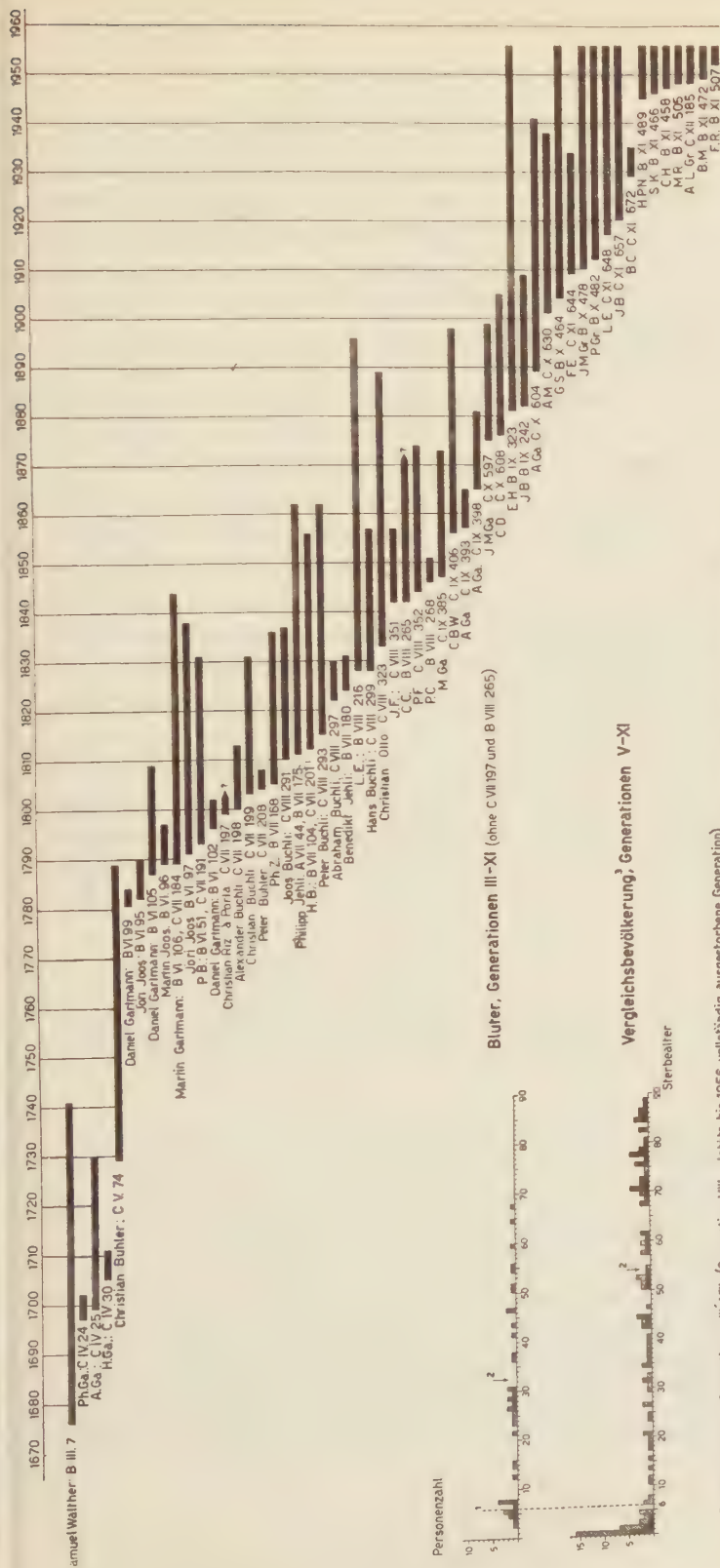
Als Vergleichsmaterial zu den Blutern wurden die männlichen Nachkommen des Ehepaares III. 3 und III. 4 in den Generationen V bis XI aus dem Teil A der Nachfahrentafel zugezogen. Die Zusammenstellung des Materials wurde wie für Tab. 8 durchgeführt, wobei jedoch A IV. 1, als nahe mit dem haemophilen Familienzweig verwandt, wie auch alle Personen mit unbekanntem Todesdatum, ausgelassen worden sind.

Bei Berechnung des mittleren Sterbealters der Bluter im Vergleich zu demjenigen der Kontrollbevölkerung muß das mögliche Vorkommen der nicht manifesten Bluter unter den vor dem 6. Lebensjahr verstorbenen Söhnen der Konduktorinnen (vgl. S. 53 und 83) berücksichtigt werden. Ein Teil dieser nicht manifesten Bluter ist vielleicht unter den vor dem

FIG.2 STERBEALTER DER BLUTER, DER BLUTERMUETTER UND DER VERGLEICHSPERSONEN, nur Personen mit bekanntem Todesalter sind eingezeichnet, bei den Blutern sind C VII.197 und B VIII.265 nicht eingezeichnet
DURATION OF LIFE OF HEMOPHILIACS, OF THEIR MOTHERS AND OF PERSONS CHOSEN FOR THE PURPOSE OF COMPARISON, only persons whose duration of life is known are included: of the hemophiliacs C VII.197 and B VIII.265 are not recorded.



■ - Personen aus den Generationen III - VIII (Generation VIII = letzte bis 1955 vollständig ausgestorbene Generation)
▨ - verstorbene Personen aus den Generationen IX - XI
□ - Unter den vor dem 6. Lebensjahr verstorbenen Söhnen der Konkurrentinnen konnten sich auch nicht-diagnostizierte Haemophiliefälle befinden, die sich nicht manifestiert haben.
2 Vergleichspersonen ohne haemophile Vererbung
3 Mittleres Sterbealter ab 6 Lebensjahr berechnet
■ - Persons of generations III - VIII. (Generation VIII = last generation with no survivors in 1955)
▨ - Among those sons of carriers who died before the completion of their 6th year of life unrecognized cases of hemophilia may have existed
□ - Deceased persons of generation IX - XI



- Personen aus den Generationen III-VIII (Generation VIII = letzte bis 1956 vollständig ausgestorbene Generation).
 - Personen aus den Generationen IX-XI.
 - Die Lebensdauer wurde als mittlere Altersgrenze für die klinische Manifestation der Haemophilie im Tenner Bluterstamm angenommen. Unter den jüngeren verstorbenen Söhnen der Konkurrentinnen konnten sich noch nicht manifeste Haemophilie befunden haben. Daher kann die Zahl der vor dem 6. Lebensjahr verstorbenen Bluter nicht als genau angesehen werden.
 - Mittleres Sterbalt, berechnet ab 6. Lebensjahr.
 - Männliche Nachkommenschaft aus einem Seitenzweig der Verwandtschaft der Tenner Bluter, jedoch ohne haemophile Vererbung. Nur Männer mit bekanntem Todesalter sind eingezeichnet.
- DURATION OF LIFE OF THE HEMOPHILIACS OF TENNA AND OF A CONTROL POPULATION**
- Persons of generations III-VIII (Generation VIII = last generation with no survivors in 1956).
 - Deceased persons of generations IX-XI.
 - The 6th year of life was assumed as the mean age limit for the clinical manifestation of hemophilia in the hemophiliacs of Tenna. Among the sons of female carriers, the age limit for the clinical manifestation of hemophilia in the hemophiliacs of Tenna was assumed as the mean age limit for the clinical manifestation of hemophilia in the hemophiliacs of Tenna. Hence, the number of hemophiliacs deceased before the 6th year of life cannot be considered as accurate.
 - Mean duration of life, calculated from 6th year of life.
 - Male descendants from a side-branch of relatives of Tenna hemophiliacs without hemophilic heredity. Only men, whose date of death was known, are included.

6. Lebensjahr verstorbenen Bluterbrüdern erfaßt worden. Das 6. Lebensjahr als die von uns angenommene Grenze für die klinische Manifestation der Haemophilie im Tenner Bluterstamm haben wir in den 3 Sterbealterdiagrammen der Männer besonders eingezeichnet. Das berechnete mittlere Sterbealter nach dem 6. Lebensjahr stellt selbstverständlich keine absolute Vergleichsgröße dar und soll lediglich zur Veranschaulichung der Sterblichkeitsunterschiede dienen.

Nachdem in der vorliegenden Arbeit nicht nur die Fertilität der Bluter, sondern auch diejenige der Blutmütter berücksichtigt wird, scheint uns auch die Sterblichkeit der Blutmütter von Interesse zu sein. Das Sterbealter der Blutmütter und dasjenige der als Vergleich zugezogenen Mütter aus dem Teil A der Nachfahrentafel ist aus Fig. 2 ersichtlich. Das Vergleichsmaterial wurde ähnlich wie für Tab. 10 gewählt, wobei ex definitione kinderlose Frauen und solche mit unbekanntem Sterbealter ausgelassen wurden.

In Fig. 3 werden die Angaben über die Lebensdauer der Tenner Bluter aus Tab. 13 graphisch dargestellt, wobei das relativ hohe Lebensalter zahlreicher Bluter und der zeitlich eher in Zunahme begriffene Bestand an Bluterfällen veranschaulicht wird.

Für eine eingehendere Analyse über die Sterblichkeit im Bluterstamm von Tenna wird auf die Arbeit von ROSIN ET AL. (1958) verwiesen, es kann aber schon hier vermerkt werden, daß *der Selektionsnachteil der erhöhten Sterblichkeit der Bluter durch eine größere Kinderzahl in den Bluterfamilien aufgewogen zu sein scheint.*

6. Farbsehen- und CN-Geruchssinnprüfung bei den Blutern aus dem Stamm von Tenna und bei ihren Familien

Farbensinnanomalien werden X-chromosomal vererbt. Im Hinblick auf eine mögliche Koppelung mit dem ebenfalls X-chromosomal vererbten Haemophilie B-Gen und auf die sich daraus ergebenden statistisch-genetischen Berechnungsmöglichkeiten wurden sämtliche in der Schweiz lebenden Bluter sowie ihre nächsten Angehörigen einer Farbsinnprüfung unterzogen. Die Prüfung erfolgte mittels der ISHIHARA-Tafeln und umfaßte insgesamt 52 Personen, darunter 11 Bluter. Es konnten keine sicheren Farbsinnanomalien festgestellt werden. Die untersuchten Personen sind in unserer Nachfahrentafel bezeichnet. Für detaillierte Angaben wird auf die Arbeit HUSER, MOOR-JANKOWSKI, TRUOG und GEIGER (1958) verwiesen.

Auf persönliche Anregung von Dr. A. E. MOURANT führten wir die Geruchsinnsprüfung auf Blausäure durch.

Die Tatsache, daß eine Anzahl Menschen, in erster Linie Männer, den Geruch von Blausäure nicht zu identifizieren vermögen, veranlaßte MOURANT (1950) zur Hypothese einer Geschlechtskoppelung. KIRK und STENHOUSE (1953) sind diesem Problem nachgegangen: unter 132 Männern fanden sie 24 und unter 112 Frauen 5, die nicht in der Lage waren, die Blausäure vom Wasser dem Geruch nach zu unterscheiden. Diese Zahlen scheinen auf eine X-chromosomale Vererbung des CN-Geruchsempfindens hinzuweisen.

Unsere Untersuchungsmethode entsprach derjenigen von KIRK und STENHOUSE (1953). ALLISON (1953) und BÜCHI (1957). Vier verschlossene Fläschchen enthielten eine 20% Lösung von analysenreinem Kaliumcyanid (Analar), und vier gleiche Fläschchen enthielten destilliertes Wasser. Die Fläschchen mußten von den Probanden richtig in zwei Gruppen geschieden werden, nachdem zuvor der normale Geruchssinn mit aqua Laurocerasi Pharmacopea Helvetica V. geprüft worden war.

Unter den 50 untersuchten Probanden befanden sich 9 Bluter. Die untersuchten Personen sind in unserer Nachfahrentafel bezeichnet.

Bei den immer noch ungenügenden Kenntnissen über die Vererbung der CN-Geruchsinnsanomalie sind unsere Ergebnisse schwierig zu interpretieren. Jedenfalls geht der Erbgang einer CN-Geruchsinnsanomalie im Stamm der Bluter von Tenna nicht parallel mit der Vererbung des Haemophilie B-Gens.

Für detaillierte Angaben wird auf die Arbeit HUSER, MOOR-JANKOWSKI, TRUOG und GEIGER (1958) verwiesen.

Das Haemophilie B-Gen des Bluterstammes von Tenna ist demnach weder mit einer Farbsinnsanomalie noch mit einer CN-Geruchssinnsanomalie gekoppelt.

7. Darstellung der Ergebnisse

A. Besprechung der vollständigen Nachfahrentafel des Bluterstammes von Tenna

1) Einteilung.

Die vollständige Nachfahrentafel (im Anhang) des ersten bekannten Stammelternpaares der Bluter von Tenna enthält alle 3072 von uns erfaßten Personen aus diesem Bluterstamm. Übersichtshalber wurde die Nachfahrentafel von der III. Generation an in 3 Teile gegliedert, welche den 3 Hauptstämmen der späteren Generationen entsprechen:

Teil A = die Nachkommen von III. 4 kopuliert mit III. 3

Teil B = die Nachkommen von III. 7 kopuliert mit III. 6 und mit III. 8

Teil C = die Nachkommen von III. 10 kopuliert mit III. 9

Im Teil A konnte keine haemophile Vererbung nachgewiesen werden. Es tritt dort nur der sporadische Bluter A IX. 10 auf. In den Teilen B und C kommen zahlreiche Bluterfälle vor; der dort angenommene haemophile Vererbungsweg wurde jeweils durch einen dicken Verbindungsstrich veranschaulicht.

Die im Teil A aufgeführten Personen unterscheiden sich von den übrigen Nachkommen des Stammelternpaares aus den Teilen B und C *nur* durch Fehlen der haemophilen Vererbung. *Alle 3 Nachfahrenstämme lebten und leben unter gleichen Umweltsverhältnissen*, worunter wir hier die geographische Verteilung (vgl. Tab. 1), das Verhältnis von Dorf- zu Stadteinwohnern (vgl. Wohnorte im Namenverzeichnis) und die soziale Stellung verstehen. Ein großer Teil der Nachkommen aus allen 3 Nachfahrenstämmen gehört zu der weitgehend homogenen Walserbevölkerung (vgl. S. 5–10), wobei die vorwiegend in den letzten Generationen erfolgte Durchmischung mit anderen Volksgruppen, in allen 3 Stämmen ungefähr die gleichen Ausmaße aufweist.

Somit bietet der Teil A ein normales Kontrollmaterial zum Vergleich mit den Teilen B und C, welche die haemophile Vererbung aufweisen.

Die Nachfahrentafel enthält in ihren 3 Teilen außer allen eruierbaren Nachkommen des ersten Stammelternpaares der Bluter von Tenna auch alle angeheirateten Personen. Die Ehen, bei welchen die Vorfahren beider Ehepartner in der Nachfahrentafel aufgeführt sind, lassen sich jeweils auf gemeinsame Vorfahren zurückführen und sind somit consanguin. Folglich sind alle Ehen mit Verweisnummern (siehe weiter unten in: 2) *Darstellungsweise*) consanguin. In Fällen, bei welchen die Consanguinität direkt aus der Nachfahrentafel ersichtlich ist, wurde auf das doppelte Aufzeichnen mit Verweisnummern verzichtet, z. B. bei A VII. 8 kopuliert mit A VII. 9.

Es soll erwähnt werden, daß es in der Nachfahrentafel auch zahlreiche consanguine Ehen gibt, die als solche anhand der Nachfahrentafel nicht erkannt werden können, da ihre gemeinsamen Vorfahren dort nicht erfaßt wurden, weil sie nicht zum Bluterstamm gehören. Somit ist aber auch der Anteil der consanguinen Ehen an der Nachfahrentafel bedeutend größer, als dies aus der hier gebotenen Darstellung ersichtlich ist. Die erfaßte Bevölkerung stammt aber auch größtenteils aus den Endogamiegebieten Graubündens (vgl. S. 5–10 und Tab. 1).

Zum besseren Überblick der Vererbungsverhältnisse wurden Tafel 5 und 6 als Auszüge aus der vollständigen Nachfahrentafel erstellt.

2) Darstellungsweise.

Numerierung der Generationen:

Die Nachfahrentafel der Bluter von Tenna erfaßt 13 Generationen; diese sind am Anfang und am Ende jeder genealogischen Tafel mit römischen Zahlen angegeben.

Laufende Numerierung der einzelnen Personen:

Die einzelnen Personen sind mit arabischen Zahlen numeriert. Die Numerierung ist innerhalb jeder Generation durchlaufend. Sie beginnt jeweils im Teil A der Nachfahrentafel und setzt sich in den Teilen B und C fort. Als Nachtrag sind in einigen Fällen die arabischen Zahlen zusätzlich mit kleinen Buchstaben versehen, z.B. 31a, 31b; ferner wurde für die als Nachtrag eingefügten Nachkommen des Ehepaares B VI. 35, B VI. 36, ab VIII. Nachfahrentafelgeneration, eine zusätzliche mit * versehene laufende Numerierung mit arabischen Zahlen eingeführt, die in jeder Generation mit 1 beginnt, z.B. 1*, 2*, 3*. Alle Nachtragsnummern sind für jede Generation am Ende jedes Teiles der Nachfahrentafel ausgeschrieben, um die Fehlermöglichkeit beim Auszählen zu verringern. Die Nachträge sind nur auf technische Ursachen beim Aufzeichnen der Nachfahrentafel zurückzuführen, und zwar wurden sie bei Vervollständigung des Aufnahmемaterials eingeführt. Wir zogen vor, auf die einheitliche, durchgehende Numerierung zu verzichten, da ihre nachträgliche Einführung infolge der vielen Verweise kompliziert gewesen wäre und eine zusätzliche Fehlerquelle bilden würde. *Die Nachtragsposten unterscheiden sich in nichts von den übrigen Posten der Nachfahrentafel.*

Die in der *Nachfahrentafel* aufgezeichneten Personen sind meist nach ihren Geburtsdaten geordnet. In mehreren Fällen konnte jedoch diese Anordnung aus Gründen der übersichtlichen Darstellung der ganzen Tafel oder infolge späterer Nachträge nicht aufrechterhalten werden.

In den *Auszügen aus der Nachfahrentafel* (Tafel 5 und 6) wurde die Anordnung nach Geburtsdaten ausnahmslos eingehalten; es wurde dadurch in einigen Fällen die Reihenfolge der Standortnummern verschoben, z.B. in der Tafel 5 kommt in der IV. Generation die Standortnummer 19 vor der Nummer 10.

Von der laufenden arabischen Numerierung sind in der Nachfahrentafel die einzelnen Nummern nur in den folgenden Fällen ausgeschrieben:

- die erste und die letzte Nummer pro Generation jeweils im Teil A, B und C,
- jede zehnte Nummer,
- die Nummer der im Text besprochenen Personen; diese Nummern sind in der Nachfahrentafel jeweils unterstrichen,
- jede wiederholt auftretende Person, wobei jeweils alle ihre Standortnummern in der Nachfahrentafel ausgeschrieben sind,
- alle Nachtragsnummern, ob mit kleinen Buchstaben oder mit * versehen,
- jeweils eine Nummer unmittelbar vor einer Nachtragsnummer.

Verweise in der Nachfahrentafel:

Die in der Nachfahrentafel wiederholt auftretenden Personen sind jeweils mit Verweisen auf ihre anderweitigen Standortnummern versehen. Es ergeben sich dabei folgende Möglichkeiten:

- Verweis auf dieselbe Person in der gleichen Generation des gleichen Teiles der Nachfahrentafel, z.B. im Teil A, Generation IX. 20, 130
- Verweis auf dieselbe Person in einer anderen Generation des gleichen Teiles der Nachfahrentafel, z.B. im Teil B, Generation X. 266, XI. 512.
- Verweis auf dieselbe Person in einem anderen Teil der Nachfahrentafel, z.B. im Teil A, Generation IX. 67, B IX. 335

Bei Verweisen auf die im Text besprochenen Personen ist nur die Standortnummer, unter welcher die Person besprochen wird, unterstrichen, z.B. im Teil C, Generation VII. 184, B VI. 106, d.h. die Person wird unter Nummer B VI, 106 im Text besprochen.

Weitere Angaben über die Verweise sind der Legende in der Nachfahrentafel zu entnehmen.

B. Einzelbeschreibung der diskutierten Fälle im speziellen Teil der Arbeit

Folgende Fälle sind im speziellen Teil der Arbeit beschrieben worden:

- Bluter;
- Personen, die in der bisherigen Literatur irrtümlicherweise als Bluter, «Teilbluter» oder «rudimentäre» Bluter bezeichnet wurden;

- Frauen, die in der bisherigen Literatur irrtümlicherweise als «Teilbluterinnen» oder als heterozygote Konduktorinnen mit Blutungstendenz bezeichnet wurden;
- alle 1956 57 gerinnungsphysiologisch untersuchten Personen;
- gemeinsame Vorfahren der Teile A, B und C der Nachfahrentafel;
- Personen, die für die genealogischen Nachforschungen von besonderer Bedeutung gewesen sind;
- Personen, die in der früheren Literatur ohne genaue Angaben mit dem Bluterstamm von Tenna in Verbindung gebracht wurden.

Einfachheitshalber wurde in der Arbeit eine einheitliche Schreibweise der Namen eingeführt, wenn auch in den Kirchenbüchern die Orthographie der gleichen Geschlechtsnamen variiert; so schreiben wir z.B. konsequent BÜHLER und nicht BÜELER, BÜEHLER oder BIELER. Bei den Personen mit heute lebenden Nachkommen in männlicher Linie wurde nur der erste Buchstabe des Namens angegeben.

Die vor unserer Bestandesaufnahme verstorbenen Personen aus dem Bluterstamm von Tenna werden *Propositi*, die noch lebenden *Probanden* benannt. Die Krankengeschichten der Propositi werden als *Katamnesen*, diejenigen der Probanden als *Anamnesen* bezeichnet.

Die Bluter von Tenna stellen den ältesten bekannten und meist beschriebenen Bluterstamm dar. Bei der Beschreibung der diskutierten Fälle im speziellen Teil der Arbeit beziehen wir uns auf die bisherigen Originalbeschreibungen, wobei jeweils nur der betreffende Autor, nicht aber das Jahr seiner Veröffentlichung genannt wird. Die genauen bibliographischen Angaben sind der Literaturbesprechung (S. 10 ff.) und der Bibliographie zu entnehmen.

Im Verlaufe unserer Nachforschungen gelang es uns, zahlreiche Irrtümer in den früheren Beschreibungen, die zum Teil ganze Familienzweige betrafen, zu korrigieren. Diese Korrekturen sind aus dem Vergleich unserer Nachfahrentafel mit den früheren Veröffentlichungen ersichtlich. Im speziellen Teil der Arbeit werden sie nur dann erwähnt, wenn sie für die haemophile Vererbung wesentlich oder für die Beschreibung der einzelnen Bluter von Bedeutung sind.

Die im speziellen Teil der Arbeit verwendeten Abkürzungen sind mit denjenigen im Namenverzeichnis identisch. Sie sind bei der hier folgenden Beschreibung des Namenverzeichnisses angegeben.

**C. Besprechung des Namenverzeichnisses der 3072 erfaßten Nachkommen
des ersten bekannten Stammelternpaares des Bluterstammes von Tenna**

Das Namenverzeichnis enthält die genauen Personalangaben aller in der Arbeit erfaßten Personen. Zusätzlich sind die Namen der in der Tafel 4 auftretenden Personen angegeben.

Als Autoren für das Namenverzeichnis zeichnen G. TRUOG, M. SCHNEEBERGER und J. K. MOOR-JANKOWSKI aus dem Institut de Génétique médicale (P.D. Dr. D. KLEIN), Clinique Universitaire d'Ophtalmologie, Genève (Dir.: Prof. A. FRANCESCHETTI).

Das Namenverzeichnis wird nicht veröffentlicht, wurde jedoch den folgenden schweizerischen und ausländischen Instituten überreicht:

- 2 Exemplare: Institut de Génétique médicale, Clinique Universitaire d'Ophtalmologie, rue Alcide Jentzer, Genève.
- 1 Exemplar: The University Institute for Human Genetics, Copenhagen N, Denmark.
- 1 Exemplar: Staatsarchiv von Graubünden, Chur.
- 1 Exemplar: The Galton Laboratory, University College, Gower Street, London, W.C. 1.
- 1 Exemplar: Institute for the Study of Human Variations, Columbia University, 413 West 117 Street, New York 27, N. Y.
- 1 Exemplar: Max-Planck-Institut für vergleichende Erbbiologie und Erbpathologie, Ehrenbergstraße 26 28, Berlin-Dahlem

Ein Exemplar kann vom Institut de Génétique médicale in Genf leihweise bezogen werden. Übrige Institute handeln nach ihren Vorschriften.

Das Namenverzeichnis gilt als Manuskript und soll nur unter Wahrung des üblichen ärztlichen Geheimnisses benützt werden.

Folgende Abkürzungen werden im Namenverzeichnis verwendet und bei der Beschreibung der Fälle im allgemeinen und im speziellen Teil der Arbeit übernommen:

- K. = Kirchenbuch (Tauf-, Ehe- und Sterberegister)
- Z. = Zivilstandsregister
- E. = Einwohnerkontrolle
- T. = Tenna
- S. = Safien (d.h. Safien-Platz, Safien-Neukirch, Safien-Thalkirch)
- Ve. = Versam
- Val. = Valendas
- P. = uns persönlich als Patient bekannte Person

1	Martin	H	1741-1803	1773	K.S.	Schreiber u. Ratsherr
2	Menga	Juon	1754-1819		K.S.	
3	Albrecht	H	1744-1746		K.S.	
4	Abraham	Brehm	+1794/41jährig		K.S.	Kirchenvogt
5	Ursula	H	1757-1839		K.S.	v. Zälän
6	Wieland	B	1740-1807	1768	K.S.	Kirchenvogt
7	Barbara	H	1747-1807		K.S.	
8, B V. 26	Albrecht	"	1753-1807		K.S.	
9, B V. 27	Maria	Walther	1760-1844		K.S. & K.T.	
10	Leonhard	G	1754	1780	K.S.	
11	Elsbeth	H	1750		K.S.	
12	Tochter	G	1731+		K.T.	
13	Samuel	"	1732		K.T.	
14	Mathäus	"	1734-1736		K.T.	
15	Mathäus	"	1737	1780	K.T.	v. Parpan
16	Margarethe	Dagascha			K.T.	
17	Joos	G	1742-1804	1778	K.T.	
18	Elsbeth	Weibel	1748-1790		K.T.	
19	Sohn	Gartmann	1733+		K.T.	
20	Christina	"	1734		K.T.	
21	Anna Maria	"	1736		K.T.	
22	Samuel	"	1738+		K.T.	
23	Samuel	Walther	1754	1782	K. Chur	v. Araschgen/Malix
24	Christina	Schocher			K. Chur	
25	Hans	Walther	1758+		K.T. & K.S.	
26, A V. 8	Albrecht	B	1753-1807		K.S.	
27, A V. 9	Maria	Walther	1760-1844		K.S. & K.T.	
28	Joos	Buchli	1716-1780	1759	K. Val.	
29	Anna Maria	Walther	1741-1775		K. Val.	
30	Samuel	"	1745-1799	1780	K.T. & K. Val.	
31	Katharina	Brehm	1743-1820		K.T. & K. Val.	
31a	Johannes	Walther	1747-1787	1773	K.T. & K. Val.	
31b	Ursula	Brehm			K.T. & K. Val.	
32	Barbara	Walther	1753-1754		K. Val.	
33	Ursula	"	1751-1754		K.T.	
34	Anna Barbara	"	1754+		K.T.	
35	Ursula	"	1755-1757		K.T.	
36	Abraham	"	1757-1841	1786	K.T.	
37	Barbara	Gartmann	1753-1839		K.T.	
38	Ursula	Walther	1760-1766		K.T.	
39	Anna	"	1763-1765		K.T.	

Fig. 4.

Eine Seite aus dem Namenverzeichnis als Beispiel der Darstellungsweise.
Für die Veröffentlichung sind bei den Personen mit heute lebenden Nachkommen in männlicher Linie die Namen ausgestrichen.

Sample page from the Register of Names. The names of persons with descendants in the male line living to-day are blacked out here.

P.v.T. = uns persönlich als Patient bekannte Person, in
Tenna beheimatet (desgleichen für S., Ve., Val.)
pers. M. bzw. P.M. = persönliche Mitteilung
.... = fehlende Angabe
Geburtsdatum mit
† versehen, z.B.
1731 † = geboren und gestorben im gleichen Jahr
† vor dem Todes-
datum, z.B. †1684 = nur Todesdatum bekannt

Das Namenverzeichnis ist nach Generationen aufgeteilt. Innerhalb jeder Generation sind die Personalangaben für die Teile A, B und C der Nachfahrentafel durch einen roten Strich voneinander abgeteilt. Die aufgeführten Personen sind nach ihren Standortnummern aus der Nachfahrentafel geordnet und die wiederholt auftretenden jeweils mit allen ihren Standortnummern versehen. Die Ehepaare sind durch ein Kopulationszeichen verbunden.

Von jeder Person wird angegeben:

Standortnummer	Vorname	Name	
Geburtsjahr ¹⁾	Todesjahr ¹⁾	Kopulationsjahr	Quelle
Heimatort ²⁾	(Bürgerort)	Wohnort ³⁾	und Bemerkungen.

Das Fehlen von Angaben bedeutet, daß sie in den Originalquellen nicht eruierbar gewesen sind.

¹⁾ Bei allen aus den Kirchenbüchern vor 1837 übernommenen Angaben sind anstelle der Geburtsdaten die Taufdaten und anstelle der Sterbedaten die Begräbnisdaten angegeben. Es ergeben sich dadurch nur geringe Ungenauigkeiten, da es im Bündnerland Brauch gewesen ist, die Neugeborenen in den ersten Lebenstagen zu taufen.

²⁾ Bei den verstorbenen Personen, für welche kein Heimatort angegeben wurde, entspricht dieser im allgemeinen dem Ort, in welchem diese Person in das Kirchenbuch bzw. in das Zivilstandsregister aufgenommen wurde.

³⁾ Bei Angaben aus den Einwohnerkontrollen ist jeweils der Wohnort der betreffenden Person mit dem Ort der Einwohnerkontrolle identisch.

8. Diskussion

Der Stamm der Bluter von Tenna mit den 55 seit dem 17. Jahrh. erfaßten Blutern ist der größte und älteste der bekannten Bluterstämme. Er ist zugleich der erste große Bluterstamm, dessen Nachkommen nach den neuesten Erkenntnissen und weitgehend vollzählig untersucht wurden.

Im Verlaufe unserer Bestandesaufnahme konnten fast alle Nachkommen der Tenner Bluter mit Möglichkeit der haemophilen Vererbung untersucht und 5 neue Bluterfälle erfaßt werden.

Anhand des so zusammengestellten und im allgemeinen und speziellen Teil dieser Arbeit genau besprochenen Materials soll hier die Haemophilie im Bluterstamm von Tenna zusammenfassend besprochen werden.

A. Erscheinungsform der Haemophilie bei den Blutern aus dem Stamm von Tenna

1) *Bemerkungen zum familiären Krankheitstypus der Haemophilie. Gerinnungsphysiologische Befunde und ihre klinische Ausprägung.*

Von der Variabilität des haemophilen Krankheitsbildes mit seinen schweren und leichten Formen ausgehend, nahm bereits BAUER (1922) an, daß «die Haemophilie bedingende Gen in verschiedener quantitativer und vielleicht auch qualitativer Abstufung vorkommt, und daß die verschiedenen Abstufungen der äußeren Merkmalsbildung durch solche quantitative Abstufungen der Gensubstanz, daß schließlich innerhalb der gleichen Familie weitgehend gleiche Merkmalsausbildung durch die gleiche Quantität und Qualität der Gensubstanz bedingt sind».

Auf diese theoretischen Überlegungen von BAUER stützte sich SCHLOESSMANN (1930), als er anhand seines großen Krankengutes den Begriff des «familiären Krankheitstypus der Haemophilie» prägte. Nach seinen Beobachtungen äußert sich der familiäre Charakter des Leidens bei allen Nachkommen eines Bluterstammes, und zwar weniger durch eine quantitative Ausprägung als vielmehr durch das Übereinstimmen der folgenden drei Merkmale:

1. die Art der Blutungserscheinungen, d.h. Vorhandensein oder Fehlen gewisser markanter Blutungsarten,
2. der zeitliche Beginn und zum Teil auch das Abklingen der Blutungsbereitschaft mit dem Alter,
3. der Grad der Gerinnungszeitverzögerung.

SCHLOESSMANN stützt sich dabei auf seine eigenen Untersuchungen mehrerer Bluterfamilien und beruft sich auch auf den Bluterstamm von Tenna, bei welchem er allerdings

zur Bestätigung seiner Theorie das familiäre Fehlen von Gelenkblutungen annimmt, welches von uns widerlegt wurde (vgl. S. 19).

Auch HALDANE (1935) wurde auf die familiären Unterschiede im haemophilen Krankheitsbild aufmerksam und erwog die Möglichkeit, diese durch die multiple Allelie der Haemophilie zu erklären.

Mit der Verfeinerung der Laboratoriumstechnik konnte dann in den letzten Jahren die Haemophilie A als Faktor VIII-Mangel und die Haemophilie B als Faktor IX-Mangel differenziert werden (für Nomenklatur vgl. S. 44). Beide Erkrankungen sind klinisch und in bezug auf die Vererbung nicht zu unterscheiden, und bei den beiden kommen milde bis schwere Krankheitsformen vor.

Die gerinnungsphysiologisch untersuchten 10 Tenner Bluter weisen normale Faktor VIII-Werte und einen stark verminderten Faktor IX-Gehalt von 2,5 bis 6% der Norm auf, was einen engen Streubereich darstellt und der mittelschweren Form der Haemophilie B entspricht. Somit wird, im Sinne der von SCHLOESSMANN (1930) postulierten familiären Übereinstimmung der Gerinnungszeitverzögerung, die *konstante familiäre Ausprägung des Faktor IX-Mangels bei einem weitverzweigten Bluterstamm, dessen gemeinsame Abstammung zum Teil um 9 Generationen zurückliegt* (vgl. Tafel 6), festgestellt.

Die familiäre Konstanz der, von Familie zu Familie verschiedenen, Faktor IX-Mangelwerte wurde bereits im Gerinnungsphysiologischen Labor von KOLLER bei kleinen Bluterfamilien beobachtet (M. GEIGER, persönliche Mitteilung). Die Bestätigung dieser Beobachtungen auf der größeren Basis unseres Untersuchungsgutes scheint uns zu allgemeingültigen Schlußfolgerungen zu berechtigen. In Anlehnung an die von BRINKHOUS und GRAHAM (1954) für die Haemophilie A postulierte Allelserie nehmen wir an, daß auch bei der Haemophilie B der Grad der Verminderung von Faktor IX im Blut erbmäßig in einer Allelserie verankert ist.

Somit könnte für die Haemophilie A und B je eine Allelserie angenommen werden, wobei, in Anlehnung an VOGEL (1955a), die beiden Serien im Verhältnis der Pseudoallelie stehen würden.

Allerdings wird in unserem Beobachtungsgut, im Gegensatz zu den Befunden von BRINKHOUS und GRAHAM (1954) die Schwere der klinischen Erscheinungen nicht einzig und direkt von dem Grad des Faktor IX-Mangels bestimmt. Der Konstanz der gerinnungsphysiologischen Befunde stehen bei den Tenner Blutern recht unterschiedliche klinische Krankheitsbilder gegenüber. Es kann zwar im allgemeinen, auf den ganzen Bluterstamm bezogen, auch von einer klinisch mittelschweren Form der Haemophilie gesprochen

werden, da im Tenner Bluterstamm fast alle Blutungsarten auftreten, und zwar meist nicht sehr häufig, nur selten spontan und in keinem Fall mit Folgen, welche das Ausüben der manuellen Berufe oder physische Betätigung ausschließen würden. Dennoch kann nur sehr bedingt eine familiäre Übereinstimmung der Blutungsmerkmale im Sinne von SCHLOESSMANN (1930) angenommen werden, da die Ausprägung der klinischen Erscheinungen beträchtliche individuelle Unterschiede feststellen läßt, auf die hier näher eingegangen wird.

Die *Art der Blutungserscheinungen* ist bei den Tenner Blutern individuell verschieden. Neben Fällen mit fast gleichmäßigem Auftreten aller Blutungsarten, wie z.B. B X. 404 oder C XI. 644, treffen wir auch solche, bei welchen trotz verhältnismäßig starken Blutungserscheinungen die eine oder andere sonst charakteristische haemophile Blutungsart vollständig fehlt, wie Nasenbluten bei C X. 630 und B XI. 505, Blutungen aus dem Mund und Suffusionen bei C XI. 657. In anderen Fällen wird das klinische Bild durch eine Blutungsart besonders stark dominiert, so durch Muskelblutungen bei B X. 482 und C XI. 657 und durch Gelenkblutungen bei B XI. 466. Die individuellen Unterschiede auch in der Stärke der Blutungstendenz ergeben sich aus dem Vergleich des verbluteten C XI. 672 mit seinen haemophilen Alters- und Zeitgenossen, die bei ähnlichen Umweltsbedingungen und therapeutischen Möglichkeiten und trotz mehrfacher Blutungen ihrer Blutungsbereitschaft nicht erlegen sind.

Der *zeitliche Beginn der klinischen Erscheinungen* weist bei den Tenner Blutern trotz meist sehr ähnlicher Umweltsverhältnisse ebenfalls eine große Variationsbreite auf, die vom 1. Lebensjahr bis zur Pubertät reicht. Als Beispiel der individuellen Unterschiede kann hier auf zwei unter gleichen Bedingungen aufwachsende Brüder hingewiesen werden, wovon einer, B XI. 505, seit dem ersten Lebensjahr an multiplen Blutungserscheinungen leidet, wogegen der andere, B XI. 507, bis zu seinem heutigen fünften Lebensjahr überhaupt keine klinisch feststellbare Blutungsbereitschaft aufweist, obwohl sein gerinnungsphysiologischer Blutuntersuchungsbefund demjenigen seines manifest haemophilen Bruders weitgehend entspricht. *Es handelt sich hier somit um einen nicht manifesten Bluter mit einem ausgesprochen haemophilen Laboratoriumsbefund.*

Auch das *Abklingen der Blutungserscheinungen mit dem Alter*, auf welches noch weiter hinten ausführlich eingegangen wird, zeigt beträchtliche individuelle Unterschiede in der Ausprägung und im zeitlichen Auftreten. So sind bei C X. 630, der in früher Jugend unter fast allen Blutungsarten

stark gelitten hat, seit dem 20. Lebensjahr überhaupt keine Blutungen mehr aufgetreten. Ähnlich sind C XI. 648 und B X. 478, beide in der Jugend stark mit Blutungserscheinungen behaftet, seit ihrem 30. resp. 36. Lebensjahr blutungsfrei geblieben. Dagegen zeigen der 53jährige B X. 464 und der 45jährige B X. 482 nur eine teilweise Abnahme der Blutungsbereitschaft, und der 75jährige B XI. 323 leidet noch gelegentlich an Suffusionen und Haematomen, wenn auch seine Blutungstendenz nie sehr stark gewesen sein mußte, da er den Wagnerberuf ausüben konnte.

Die Unterschiede in den klinischen Manifestationen bei den Tenner Blutern können nicht durch die ungefähr gleichen Umweltsverhältnisse bedingt sein. In einigen wenigen Fällen mag wohl für eine bestimmte Blutungserscheinung ein nur zufälliger auslösender Umstand bestimmend gewesen sein, wie z.B. bei B X. 482 der Stoß in die Magengegend, welcher eine Magenblutung hervorrief, die jedoch in diesem Falle sicherlich nicht als Symptom einer visceralen Blutungstendenz des Probanden ausgelegt werden kann. In den meisten Fällen ist es aber denkbar, daß die unterschiedliche klinische Ausprägung bei gleichbleibenden Faktor IX-Werten durch das zum Teil sicher sehr verschiedene genetische Milieu der teilweise nur sehr entfernt verwandten Bluter bedingt wird, so daß die Unterschiede im klinischen Krankheitsbild auf konstitutionelle Differenzen zurückzuführen sind.

2. Zeitliche Änderungen der Blutungsneigung bei den Blutern aus dem Stamm von Tenna

a) Abnahme der Blutungserscheinungen mit dem Alter

Wie bereits in der Diskussion unserer Ergebnisse kurz erwähnt, konnte bei einigen Tenner Blutern die Abnahme oder sogar ein vollständiges Abklingen der Blutungserscheinungen mit dem Alter festgestellt werden. Es sind dies C X. 630, B X. 464, B X. 478, B X. 482 und C XI. 648, also 5 von den 14 Blutern mit vollständig aufgenommener Krankengeschichte, wobei unter den restlichen 9 zur Zeit unserer Bestandesaufnahme nur C XI. 657 im Erwachsenenalter steht und die übrigen 8 die Pubertät noch nicht erreicht haben (vgl. Tab. 13).

In der umfangreichen Literatur, welche die Haemophilie unter den Gesichtspunkten der neuesten Errungenschaften der Gerinnungsforschung behandelt, fanden wir keine Beobachtungen über Änderung des haemophilen Geschehens im Lebenslauf. Dagegen wird in der Monographie von

SCHLOESSMANN (1930), die auf großen klinischen Erfahrungen des Autors basiert, der Rückgang der haemophilen Erscheinungen als «nach dem 30. Lebensjahr wohl in allen Fällen deutlich» (S. 228) angegeben. Auch ANDREASSEN (1943, S. 34 und 101) stellt in seinem großen für Dänemark repräsentativen Beobachtungsgut die Abnahme der Blutungstendenz nach dem 20. bis 25. Lebensjahr fest.

SCHLOESSMANN findet auch eine „allfällige und regelmäßige Steigerung der haemophilen Blutungserscheinungen in der Pubertätszeit“ (S. 288), die nach ihm durch die grosse Sterblichkeit an Verblutung zwischen dem 10. und dem 20. Lebensjahr bestätigt sein soll (vgl. Sterbealter-Tabelle von SCHLOESSMANN in unserer Tab. 12). Diese Beobachtung wird auch von ANDREASSEN (S. 33–34 und 100–101) bei den dänischen Blutern gemacht. Wie aus Tab. 13 für unser Material ersichtlich, gilt die Steigerung der Blutungserscheinungen in der Pubertätszeit für die Tenner Bluter nicht.

Wir sind allen unseren Fällen, welche die Abnahme der Blutungsbereitschaft mit dem Alter aufweisen, mit möglichst größter Sorgfalt nachgegangen.

Von dem verstorbenen C X. 630 existiert eine lückenlose Krankengeschichte bis zum vollständigen Abklingen seiner haemophilen Manifestationen, die wir, trotz ihres Umfanges, als einzigartigen Beleg in den speziellen Teil dieser Arbeit aufgenommen haben. Sie wird durch verschiedene in der Familie des Propositus aufgehobene ärztliche Atteste bestätigt, sowie auch durch die Angaben von HOESSLY-HAERLE (1930) über den damals 28jährigen Propositus und durch die Aussagen seines Bruders uns gegenüber. Aus der so zusammengestellten Katamnese ergibt sich einwandfrei, daß der Propositus in seinen Kinderjahren stark an fast allen haemophilen Blutungsarten gelitten hat, die dann mit 14 Jahren abzunehmen begannen und seit dem 20. Lebensjahr bis zum Tode im 37. Lebensjahr überhaupt nicht mehr aufgetreten sind.

Die übrigen 4 Probanden mit Abnahme der Blutungserscheinungen waren entweder von uns oder von ihren Hausärzten, die uns gut bekannt sind, behandelt und jahrelang beobachtet worden. Bei 3 davon, B X. 464, B X. 478 und B X. 482, wurde der Rückgang ihrer haemophilen Erscheinungen bereits von HOESSLY-HAERLE (1930) beschrieben; er ist inzwischen weiter fortgeschritten, wie wir es bei allen drei Probanden feststellen konnten; B X. 478 wie auch C XI. 648 sind sogar seit ihrem 36. resp. 30. Lebensjahr, zurzeit also seit 10 Jahren, vollständig blutungsfrei geblieben.

Nur bei dem 75jährigen B IX. 323, der in den Vereinigten Staaten lebt und über den wir lediglich von seinen in der Schweiz lebenden Familienmitgliedern Näheres erfahren konnten, wissen wir, daß er noch gelegentlich unter Suffusionen und Haematomen leidet, jedoch ohne Angaben, ob

diese gleich stark wie in seiner Jugend auftreten. Ebenfalls finden wir unter den früher verstorbenen Tenner Blutern solche, die in relativ fortgeschrittenem Alter verblutet sind. Auch hier wissen wir jedoch nichts über die möglichen Änderungen ihrer Blutungserscheinungen in ihrem Lebenslauf, und ein Verblutungstod ist auch bei einer bereits leichteren Blutungstendenz möglich, sobald ein entsprechend starkes Trauma gesetzt wird.

Als sichere Tatsache bleibt auf jeden Fall der Rückgang der Blutungsbereitschaft bei den 5 erwähnten Blutern mit uns vollständig bekannten Krankengeschichten. Diese Abnahme oder sogar das Verschwinden der Blutungstendenz kann nicht mit Änderung der Umweltsverhältnisse erklärt werden, auch wenn sie B X. 464 zum Teil auf größere Schonung und C XI. 648 auf seine Berufsänderung zurückführen: B X. 464 ist weiterhin in seinem für einen Bluter nicht ungefährlichen Beruf als Bauinstallateur tätig und beobachtet selbst, daß seine Verletzungen gegenwärtig nur normal lange bluten; C XI. 648 hat seinen Coiffeurberuf aufgegeben und ist Lehrer geworden, um die berufliche Verletzungsgefahr auszuschließen; die Abnahme seiner Blutungsbereitschaft ist jedoch unabhängig von der Berufsänderung aufgetreten, da der Proband in den letzten 10 Jahren bei zufälligen Verletzungen annähernd normal blutete und von den übrigen Blutungserscheinungen vollständig frei geblieben ist.

Somit sind die Umweltsbedingungen höchstens in einem nur sehr geringen Ausmaße an der von uns bei 5 Tenner Blutern festgestellten zeitlichen Abnahme der Blutungserscheinungen mitbeteiligt. Es ist uns auch nicht möglich, andere äußere Ursachen festzustellen oder nur anzunehmen.

Was den Laboratoriumsbefund anbetrifft, so zeigt er lediglich bei der älteren Generation der Bluter von Tenna leicht höhere Faktor IX-Werte, die jedoch im Bereiche der mittelschweren haemophilen Gerinnungsstörung verbleiben und für sich allein keine so starke Änderung der klinischen Ausprägung des Krankheitsgeschehens verursachen könnten.

Die bei den Tenner Blutern vorkommende Abnahme und auch das vollständige Abklingen der Blutungserscheinungen mit dem Alter kann somit nach unserem heutigen Wissen nicht erklärt werden. Es ist denkbar, daß sie mit einem noch unbekannten blutchemischen Faktor oder mit einer Gefäßkomponente zusammenhängen kann.

b) Periodische Schwankungen der Blutungserscheinungen

Die Steigerung der haemophilen Erscheinungen bei den Blutern in Abhängigkeit von der Jahreszeit ist bereits von GRANDIDIER (1877) beschrieben worden. SCHLOESSMANN (1930) findet sie in einigen Fällen seines großen

Blutermaterials, und in der neuesten Zeit schreibt DEUTSCH (1954, S.585): «Auffallend ist eine Abhängigkeit der Blutungen von der Jahreszeit».

Bei 3 Fällen aus unserem Material konnten wir diese Abhängigkeit feststellen. Bei B VII. 175 berichtete der behandelnde Arzt Dr. VIELI (bei GRANDIDIER, 1877), daß «Die Anfälle sollen... gern in der kälteren Jahreszeit eintreten». B XI. 458 weist im Frühling eine allgemein erhöhte Blutungsbereitschaft auf. C XI. 648, der seit 10 Jahren unter keinen haemophilen Blutungserscheinungen mehr leidet, hatte in der Jugend im Frühling und im Herbst fast täglich andauerndes schweres Nasenbluten.

Es scheint uns, daß die jahreszeitlichen Schwankungen mit dem haemophilen Krankheitsgeschehen nicht direkt zusammenhängen, sondern konstitutionell bedingt sind. Denn C XI. 648 leidet auch weiterhin, trotz Aufhören seiner haemophilen Blutungserscheinungen, jeden Frühling und Herbst an häufigem, wenn auch nicht sehr starkem und andauerndem Nasenbluten. In «normalen» Grenzen liegendes Nasenbluten trifft man aber relativ häufig bei Personen ohne jegliche Gerinnungsstörung, und die jahreszeitliche Steigerung kann durch eine konstitutionelle Klima- oder Jahreszeitenempfindlichkeit bedingt sein.

Anhand des Beispiels unseres Probanden C XI. 648 scheint es uns denkbar, daß *die jahreszeitlichen Schwankungen konstitutionell bedingt sein können und nur durch die zufällig vorhandene Gerinnungsstörung eine besondere klinische Ausprägung erhalten.*

Immerhin können bei gesteigerten Blutungserscheinungen in bestimmten Jahreszeiten auch äußere Einflüsse bestimmend sein. So berichtet SCHLOESSMANN (1930, S. 224) über zwei schwer haemophile Brüder aus dem Freudenstädter Bluterstamm, die im Winter regelmäßig an erheblicher Zunahme ihrer Knie- und Hüftgelenkblutungen litten. Nachdem einer der Brüder infolge schwerer haemarthrotischer Beschwerden das Haus bei Schneefall nicht mehr verlassen konnte, sind bei ihm keine Gelenkblutungen mehr im Winter aufgetreten, im Gegensatz zu seinem Bruder, welcher seine Blutungen auf das viel anstrengendere Gehen im hohen Schnee zurückführte, was auch SCHLOESSMANN als die in diesem Falle auslösende Ursache betrachtet.

Derartige Zusammenhänge werden aber wohl viel seltener vorkommen als die konstitutionell durch Empfindlichkeit auf bestimmte Jahreszeiten bedingte Blutungssteigerung.

In die Kategorie der konstitutionell bedingten Einflüsse auf die Steigerung der Blutungserscheinungen könnten ebenfalls die bei Föhnwetter und auch bei Aufregung besonders häufigen Nasenblutungen des B X. 482 und die bei Indispositionen verstärkte Blutungstendenz des B X. 464 gerechnet werden.

Ähnliche Erscheinungen wurden bereits von GRANDIDIER (1877) und auch von SCHLOESSMANN (1930) beobachtet. SCHLOESSMANN versucht sie

durch die von BERG (1921) veröffentlichten Untersuchungsergebnisse über Stoffwechselstörungen bei Haemophilen zu erklären.

Nach BERG sollen im haemophilen Blut zeitweilig größere Anhäufungen ungenügend oxydierter, saurer Stoffwechselprodukte auftreten, die zu Gefäßwandschädigung und damit zu erleichterten Blutaustritten führen. Gesteigerter Stoffwechselumsatz, Überanstrengungen, Erkältungen und auch Luftdruckschwankungen sollen diese Assimilationsstörung und Blutübersäuerung in besonderem Maß fördern.

In diesem Zusammenhang könnte auch C VIII. 299 erwähnt werden, der nach einem langen Marsch, der als eine Überanstrengung ausgelegt werden kann, von einer spontanen Oberschenkelblutung befallen wurde. Ähnliche Fälle von Spontanblutungen nach Überanstrengung werden auch von SCHLOESSMANN (1930, S. 223) beschrieben.

Es wäre zweifellos interessant, die Untersuchungen von BERG mit den modernen Untersuchungsmethoden zu wiederholen.

B. Haemophile Nachblutung

Bereits GRANDIDIER (1855) berichtet bei mehreren Haemophiliefällen ausführlich von den typischen haemophilen Nachblutungserscheinungen, wie sie dann von SCHLOESSMANN (1930) eingehend beschrieben und folgendermaßen definiert wurden (S. 33):

«Nach Oberflächenverletzungen und Verwundungen folgt hier keineswegs immer das gefürchtete unaufhaltsame Fortbluten. Es tritt vielmehr nach vorübergehender Anfangsblutung, ähnlich wie bei Normalen, ein Blutungsstillstand und damit meist eine blutungsfreie Zwischenzeit ein, die von einer halben Stunde bis zu mehreren Stunden andauern kann. Erst danach beginnt das Blut von neuem hervorzusickern und nunmehr in Form der hemmungslosen, unbeeinflussbaren, haemophilen Dauerblutung.»

In der neuesten Literatur ist die gleiche Beobachtung von DEUTSCH (1954, S. 576) gemacht worden, der die haemophile Nachblutung als «Haemophilie-Typ der Blutung» bezeichnet.

Wir konnten zahlreiche Fälle dieser Nachblutungen bei den Blutern aus dem Tenner Stamm beobachten. Sie sind im speziellen Teil dieser Arbeit, insbesondere bei den folgenden heute lebenden Blutern erwähnt: B X. 464, B X. 478, B X. 482, B XI. 489, B XI. 505 und C XI. 644. Bei den bereits verstorbenen Blutern wurden sie in folgenden Fällen beobachtet: B IX. 242, C VII. 199, C X. 604 und C X. 630.

Die Nachblutungen, auch bei inneren Blutungen, sind in einigen Fällen sogar mehrere Tage nach dem erfolgten Trauma aufgetreten, z. B. die von THORMANN (1837) beschriebene Haematocoele bei C VII. 199, die 3 Tage nach einem Stoß in die Leistegegend plötzlich in der Nacht bei

ruhiger Bettlage auftrat, oder auch die 8 Tage nach dem Trauma aufgetretene ausgedehnte Blutung in die Oberschenkelmuskulatur bei dem heute lebenden B X. 482.

Wir haben uns bei dieser charakteristischen haemophilen Erscheinung besonders aufgehalten, da sie bis jetzt weder durch die eingehenden früheren Untersuchungen, die von SCHLOESSMANN (1930, S. 32 ff. und 116 ff.) zusammengefaßt wurden, noch durch die neuesten Fortschritte der Gerinnungslehre erklärt werden konnte. *Es ist denkbar, daß auch sie mit einem bis jetzt nicht erfaßten blutchemischen Faktor oder mit einer noch unbekannten Gefäßkomponente zusammenhängen kann.*

C. Frage der Blutungserscheinungen bei den heterozygoten Konduktorinnen

Eine sorgfältige Analyse der Literaturangaben über die verstorbenen heterozygoten Konduktorinnen aus dem Bluterstamm von Tenna gibt keine Handhabe, bei ihnen eine Blutungsbereitschaft anzunehmen (vgl. S. 37 ff.). Unsere eigenen Beobachtungen und Untersuchungen aus den letzten 10 bis 20 Jahren, wie auch diejenigen der Hausärzte der Probandinnen außerhalb unseres Patientenkreises, welche zusammen den Größtteil der lebenden Konduktorinnen erfassen, geben ebenfalls keine Anhaltspunkte für die Diagnose einer Blutungsbereitschaft bei den weiblichen Heterozygoten aus dem Stamm von Tenna.

Die normalen Gerinnungsverhältnisse der Tenner Konduktorinnen wurden ferner auch durch die gerinnungsphysiologischen Laboratoriumsuntersuchungen bestätigt, welche bei der Mehrheit der 1956 lebenden Probandinnen durchgeführt wurden (vgl. 45–48 und HUSER, MOOR-JANKOWSKI, TRUOG, GEIGER, 1958).

Somit kann das Fehlen der Blutungsbereitschaft bei den heterozygoten Konduktorinnen aus dem Bluterstamm von Tenna als bewiesen angenommen werden.

Wir benützen diese eindeutige Feststellung, um uns etwas eingehender mit dem Problem der haemophilen Erscheinungen bei Frauen zu befassen.

Das Vorkommen von Haemophilie bei *homozygoten* Genträgerinnen kann seit den Kreuzungsversuchen an Hunden von BRINKHOUS und GRAHAM (1949) und den Beobachtungen an Menschen von ISRAELS, LEMPERT, GILBERTSON (1951) und MERSKEY (1951b) als bewiesen gelten. Dagegen ist die Frage von haemophilen Blutungserscheinungen bei *heterozygoten*

Genträgerinnen bis jetzt nicht völlig abgeklärt, und sie soll hier anhand von unserem Untersuchungsmaterial näher besprochen werden.

Vorerst muß die hypothetische Vorstellung der haemophilen Blutungserscheinungen bei den Konduktorinnen genauer umschrieben werden. Als solche kann unserer Ansicht nach nur eine *generalisierte Blutungstendenz mit entsprechendem Laboratoriumsbefund*, ähnlich wie bei männlichen Blutern und homozygoten weiblichen Bluterinnen, wenn auch möglicherweise in *leichterer Ausprägung*, angesehen werden.

Wir können somit mit DEUTSCH (1954. S.576) nicht einig gehen, wenn er sagt: «Schwere Menorrhagien können Folgen eines gestörten Cyclus sein, sie können aber auch die einzige Manifestation der haemophilen Anlage bei einer Konduktorin in einer Bluterfamilie darstellen». Es scheint uns vielmehr, daß Neigung zu einer *einzelnen* Blutungsart, sei es zu Menorrhagie, oder auch zu Suffusionen, oder zu Nasenbluten, schon in Anbetracht der starken Verbreitung dieser Blutungserscheinungen bei der normalen Bevölkerung nicht als Beweis einer haemophilen Blutungstendenz angesehen werden kann.

Es ist auch aus genetischen Überlegungen nicht anzunehmen, daß das gleiche Gen, welches die bei *jedem* Haemophiliefall feststellbaren *multiplen* Blutungsarten bedingt, bei den heterozygoten Konduktorinnen *nur* die Neigung zu einer *einzelnen* Blutungsart hervorrufen würde.

Die Literaturangaben über das Verhalten der heterozygoten Konduktorinnen beginnen chronologisch mit der Aussage von NASSE (1820), daß die Haemophilie «an Müttern von Blutern und überhaupt an einer weiblichen Person sich niemals äußere». Im folgenden Jahrhundert wurden zahlreiche Fälle von Blutungserscheinungen bei Frauen, darunter auch sichere Konduktorinnen, als weibliche Haemophile beschrieben. In seiner kritischen Bearbeitung des ganzen damals veröffentlichten Materials konnte jedoch BUCURA (1920) keinen der veröffentlichten Fälle als weibliche Haemophilie, auch nicht in leichtester Ausprägung, anerkennen. SCHLOESSMANN (1930), der die Ergebnisse von BUCURA für die Literatur vor 1920 bestätigt, nimmt dennoch das Vorkommen von Blutungserscheinungen bei einem Teil der Konduktorinnen an und zitiert Fälle aus der Literatur nach 1920 sowie auch aus seinem eigenen großen Patientenmaterial. Unter den 34 von ihm untersuchten Konduktorinnen fand er 16 mit einer Blutungsneigung, die er als über das Normale hinausgehend bezeichnet. Sie äußerte sich in verstärktem Nasenbluten, Menorrhagien, starken Entbindungsblutungen und Nachblutungen nach Zahnziehen, welche Erscheinungen meist gemeinsam vorkamen und bei den 7 auf Blutgerinnung geprüften

Konduktorinnen auch mit verlängerter Gerinnungszeit einhergingen. Auch unter den 6 auf Blutgerinnung untersuchten Konduktorinnen ohne klinische Blutungserscheinungen fand er bei 4 eine Gerinnungsverzögerung.

Eine eingehende Besprechung der weiteren Veröffentlichungen über Konduktorinnen mit Blutungserscheinungen ist bei ANDREASSEN (1943) zu finden. ANDREASSEN selbst fand unter den von ihm untersuchten Konduktorinnen mehrere Fälle mit klinischen Blutungserscheinungen, die er jedoch als Beweis der haemophilen Blutungstendenz ablehnt, da er sie als schwer zu objektivisieren beurteilt. Dagegen mißt er der Gerinnungszeit einen großen Wert bei und findet sie leicht verlängert bei 30 unter den 31 von ihm auf Blutgerinnung untersuchten Konduktorinnen.

Im Gegensatz zu den aufgeführten Arbeiten konnten MERSKEY und MACFARLANE (1951) keine Verzögerung der Blutgerinnung bei heterozygoten Konduktorinnen anlässlich ihrer eigens zu diesem Zwecke durchgeführten Untersuchungen feststellen.

Dagegen berichtet JÜRGENS (1952) über pathologisches Verhalten der Rekalzifizierungszeit bei den Konduktorinnen, die mit dem von ihm entwickelten Latenztestverfahren untersucht wurden.

Auch DEUTSCH (1954), der bereits die gerinnungsphysiologische Differenzierung in Haemophilie A und B berücksichtigt, beschreibt auf S. 580 die Mutter eines an Haemophilie B leidenden Patienten, die eine Verlängerung der Gerinnungszeit nach LEE-WHITE auf 16' 30'' und eine deutliche Verminderung des Prothrombinverbrauches aufwies. Er beruft sich auch auf die Feststellung von BIGGS und Mitarbeiter, die ähnlicherweise eine Gerinnungsstörung bei einer Blutermutter nachweisen konnten. In seiner weiteren sehr umfassenden Arbeit schreibt DEUTSCH (1955, S. 26), daß das Blut der Konduktorin in der Regel zwar normal gerinnt, es jedoch manchmal eine «subnormale Menge des antihaemophilen Globulins enthält und besitzt in diesen Fällen eine geringere normalisierende Wirkung auf haemophiles Blut als Normalblut und einen verminderten Prothrombinverbrauch». DEUTSCH beruft sich hiezu auf die Arbeiten von ALTHOF (1949), JÜRGENS und FERLIN (1950) und FERLIN (1951), wie auch auf die bereits von uns hier zitierte Arbeit von MERSKEY und MACFARLANE (1951), trotzdem die Autoren dieser letzten Veröffentlichung in ihren Schlußfolgerungen das Vorkommen von Gerinnungsstörungen bei Konduktorinnen mit den heute zur Verfügung stehenden Methoden als nicht nachweisbar betrachten.

Aus der Übersicht der bisherigen Literatur ergibt sich somit, daß die Frage der Blutungserscheinungen bei den heterozygoten Konduktorinnen nicht endgültig abgeklärt ist.

Die von einigen Autoren festgestellte Gerinnungszeitverlängerung wird von anderen verneint. Die Gerinnungszeitbestimmung scheint im übrigen überhaupt kein einwandfreies Erfassen der haemophilen Gerinnungsstörung zu gewährleisten (vgl. S. 42), was besonders deutlich aus dem Fall C X. 629 (s. spezieller Teil der Arbeit) ersichtlich ist.

Wenn HALDANE (1946-47) die von ANDREASSEN (1943) beschriebene leichte Gerinnungszeitverlängerung («slight protraction of the coagulation time», ANDREASSEN, S. 103) als «physiologischen Nachweis» des Haemophiliegens bei weiblichen Heterozygoten betrachtet und sie als solchen für die Berechnung der Mutationsrate mitverwendet, wenn er ferner anhand der gleichen Angaben von Verblutungsgefahr anlässlich der Sterilisationseingriffe bei Konduktorinnen spricht, so kann dies nur als Mangel an klinischen Erfahrungen und Unkenntnis der verwendeten Laboratoriumstechnik ausgelegt werden.

Immerhin sollten die Angaben mehrerer Autoren über die Konduktorinnen mit Blutungserscheinungen, zum Teil auch multipler Art, nicht übergangen werden. Nachdem nun anhand unseres Materials das Fehlen jeglicher mit den heutigen Mitteln erfaßbaren Blutungsbereitschaft bei den Konduktorinnen des weitverbreiteten Tenner Bluterstammes mit mittelschwerer Form von Haemophilie B festgestellt wurde, sollten auch bei weiteren Bluterstämmen derartige Untersuchungen durchgeführt werden. Von besonderem Interesse wären hier gerinnungsphysiologische und klinische Untersuchungen bei Stämmen mit schwerer Form von Haemophilie B, wie auch bei solchen mit verschiedenen Formen der Haemophilie A.

Zusammenfassung

Der Bluterstamm von Tenna wird nach der Bündner Walsersiedlung Tenna benannt, wo die ersten bekannten Bluter dieses Stammes im 17. Jahrh. aufgetreten sind. Die Walserbevölkerung von Tenna und der benachbarten Siedlungen Safien und Versam kann als homogen angesehen und die Gegend als ein relatives Isolat bezeichnet werden (IKIN, MOURANT, KOPEĆ, MOOR-JANKOWSKI und HUSER, 1957; MOOR-JANKOWSKI, HUSER und ROSIN, in Vorbereitung). Die Zusammensetzung der Bevölkerung hat sich seit dem 14. Jahrh. nur wenig verändert (Joos, 1946), die Bevölkerungsbewegung erfolgte fast ausschließlich im Sinne der Abwanderung (vgl. Tab. 2), und zwar meist in die umliegenden Täler. Noch heute leben die Nachkommen des ersten bekannten Stammelternpaares des Tenner Bluterstammes mehrheitlich in Tenna und Umgebung (vgl. Tab. 1), welches Gebiet auf der Karte S. 1 abgebildet ist. Die geographische Verteilung der bekannten Bluter aus dem Stamm von Tenna (vgl. Fig. 1) entspricht in großen Linien derjenigen der übrigen Bevölkerung, wenn auch

die Bluterkrankheit unter den lokalen Verhältnissen einen zusätzlichen Abwanderungsgrund bildete.

Über den Bluterstamm von Tenna liegt bereits eine umfangreiche Literatur vor; alle Originalbeschreibungen (THORMANN, 1837; VIELI, 1846; GRANDIDIER, 1855a und 1877; HOESSLI, 1885; HOESSLY-HAERLE, 1930 und Pianta, 1953) und die bedeutenderen kompilatorischen Bearbeitungen (BULLOCH und FILDES, 1912; SCHLOESSMANN, 1930 und FONIO, 1954) werden eingehend besprochen und die Irrtümer und Mißdeutungen anhand der Archivquellen und der neuesten Untersuchungsergebnisse korrigiert.

Anhand der frühen Beschreibungen aus der ersten Hälfte des 19. Jahrh. läßt sich einwandfrei feststellen, daß die haemophile Vererbung und die typischen Blutungserscheinungen bereits zu dieser Zeit in Tenna gut bekannt waren. Die Tenner gehören mit zu den ersten, welche den Ausdruck «Bluter» geprägt haben, und ihre Bezeichnung «Konduktor» für die Gen-trägerinnen wurde von GRANDIDIER (1855a) übernommen und in die Fachliteratur eingeführt.

Als Ausgangspunkt der vorliegenden Arbeit wurden die Kirchenbücher, Zivilstandsregister und Archive zahlreicher Gemeinden benützt, um eine möglichst vollständige Nachfahrentafel des ersten bekannten Stammelternpaares des Tenner Bluterstammes, Albrecht WALTHER, II.2, und Ursula BUCHLI, II.3, aus der Mitte des 17. Jahrh. aufzustellen. Die für die genealogischen Nachforschungen angewandten Methoden werden eingehend beschrieben, wie auch die dem ausländischen Leser meist unbekannte schweizerische Institution des Bürgerrechtes, welche unsere Untersuchungen ganz besonders erleichtert hat.

Die Gesamtzahl aller genealogisch erfaßten Personen ist in Tab. 3 angegeben. Die erstellte Nachfahrentafel reicht für die Bluter und die Personen mit Möglichkeit der Blutervererbung bis Ende 1956 bzw. Mitte 1957, für die übrigen erfaßten Personen bis Ende 1955. *Die Bluter und die Bluterfamilien wurden jedoch erst nach dem Aufstellen der vollständigen Nachfahrentafel bis 1955 unter den dort erfaßten Personen eruiert, wodurch alle Nachfahren, ob haemophil oder gesund, von Anfang an mit gleicher Sorgfalt verfolgt worden sind.*

Der Umfang unserer Erfassung der Nachfahren des Stammelternpaares ist aus Tab. 4 ersichtlich; unter den 3072 von uns erfaßten Nachkommen und Angeheirateten haben wir 115 Personen, meist in späteren Generationen und ohne weitere Nachkommen, infolge von Fehlen des Quellenmaterials nicht weiterverfolgen können. Diese Personen werden

im Text und in Tab. 4 als «nicht weiterverfolgbar» bezeichnet. Zusätzlich dazu haben wir beim Abschluß unserer Bestandesaufnahme 108 Personen aus den späteren Generationen nicht weiterverfolgt. Es handelt sich dabei meist um an Ausländer verheiratete Frauen, deren Weiterverfolgung mit großen Schwierigkeiten verbunden war und an unseren Ergebnissen nichts Wesentliches geändert hätten. Diese Personen werden im Text und in Tab. 4 als «nicht weiterverfolgt» bezeichnet.

Die Bluter wurden unter den in der Nachfahrentafel erfaßten Personen anhand eines eigens aufgestellten Frageschemas eruiert. Alle zur Zeit unserer Bestandesaufnahme in der Schweiz lebenden möglichen Träger des Haemophiliegens aus dem Stamm von Tenna, also die überwiegende Mehrheit der in Frage kommenden Probanden, wurden einer klinischen Untersuchung anhand unseres Frageschemas unterzogen, die in den allermeisten Fällen durch eine gerinnungsphysiologische Untersuchung vervollständigt wurde.

Unter den vor unserer Bestandesaufnahme Verstorbenen aus dem Tenner Bluterstamm bezeichnen wir alle diejenigen als Haemophile, die in den zeitgenössischen Quellen als Bluter oder an Verblutungstod Verstorbene bezeichnet sind. In Anbetracht der schon für Anfang des 19. Jahrh. nachgewiesenen guten Kenntnis des haemophilen Krankheitsgeschehens in Tenna erscheint uns diese Stellungnahme als berechtigt.

Anhand der zeitgenössischen Angaben und eigener Erhebungen lehnen wir die von HOESSLY-HAERLE (1930) behauptete atypische haemophile Vererbung und das Vorhandensein der «rudimentären Bluter» im Tenner Bluterstamm ab.

Auch das Vorkommen der haemophilen Erscheinungen bei heterozygoten Genträgerinnen aus diesem Bluterstamm, die von HOESSLY-HAERLE (1930) und PIANTA (1953) angenommen wurde, wird von uns eindeutig abgelehnt, und zwar sowohl anhand der zeitgenössischen Angaben wie auch, für die neuere Zeit, auf Grund unserer jahrelangen Beobachtungen, wiederholten klinischen Untersuchungen und gerinnungsphysiologischen Laboratoriumsbefunden.

In unseren Untersuchungen haben wir die Gerinnungszeitbestimmung im Vollblut als ungenau abgelehnt und durch fraktionierte gerinnungsphysiologische Untersuchungen ersetzt. Diese wurden durch M. GEIGER im Gerinnungsphysiologischen Labor des Kantonsspitals Zürich (Prof. F. KOLLER) durchgeführt und ergaben bei den 10 untersuchten Blutern pathologische Faktor IX-Werte von 2.5 bis 6⁰/₁₀ der Norm, was einem mittelschweren Grad der Haemophilie B entspricht.

Die sich noch im Fluß befindende Frage der Nomenklatur der Haemophilie wurde überschlagsweise besprochen.

Bei den gerinnungsphysiologisch untersuchten 11 sicheren und 33 möglichen Konduktorinnen wurden keine Gerinnungsstörungen gefunden. Für die möglichen Konduktorinnen wurde die jeweilige Wahrscheinlichkeit in % für das Vorhandensein des Haemophiliegens von S. ROSIN berechnet und ist aus Tafel 6 ersichtlich.

Der Vergleich der Faktor IX-Werte der untersuchten Bluter und Konduktorinnen ist in der Fig. auf S. 47 angegeben.

Es kann angenommen werden, daß alle zur Zeit unserer Bestandesaufnahme lebenden Bluter aus dem Tenner Stamm von uns erfaßt wurden, was durch die große Zahl der uns persönlich bekannten Personen aus diesem Bluterstamm (vgl. Tab. 5) besonders erleichtert wurde. Von den 13 in den Jahren 1952 bis 1956 lebenden Blutern konnten wir 11 persönlich klinisch untersuchen und die Untersuchungsergebnisse der uns bekannten behandelnden Hausärzte und Spitäler aufnehmen. Bei den 2 in den Vereinigten Staaten lebenden Blutern B IX. 323 und B XI. 472 mußten wir uns mit den Mitteilungen aus dem nächsten Familienkreis begnügen. 10 Bluter konnten gerinnungsphysiologisch untersucht werden.

Wir nehmen an, daß wir auch die allermeisten von den vor unserer Bestandesaufnahme verstorbenen Blutern aus dem Tenner Stamm erfaßt haben. Eine größere Unsicherheit über den Erfassungsgrad besteht lediglich für die Zeit vor 1790, aus welcher nur die Kirchenbuchvermerke und keine ärztlichen Beschreibungen vorliegen. Es gab aber in dieser Zeit, außer den uns bekannten Blutern, nur wenige theoretisch mögliche Haemophiliefälle im Tenner Bluterstamm, die alle in Tafel 2 zusammengefaßt und mit Angaben über die Wahrscheinlichkeit in % für das Vorhandensein des Haemophiliegens von S. ROSIN versehen sind. Nach 1790 kann die Erfassung der Tenner Bluter als sehr weitgehend und ab 1840 als praktisch vollständig angesehen werden. Die Wahrscheinlichkeit von haemophilen Nachkommen bei den 115 «nicht weiterverfolgbaren» und bei den 108 «nicht weiterverfolgten» Personen aus dem Tenner Bluterstamm wurde von S. ROSIN berechnet und ist in Tafel 1 angegeben. Die Möglichkeit für das Vorkommen solcher uns unbekannten Haemophilen ist jedoch äußerst gering, da die «nicht weiterverfolgbaren» Personen meist kinderlos gewesen sind, aus welchem Grunde sie nicht weiterverfolgt werden konnten, und die «nicht weiterverfolgten» Personen weisen eine Wahrscheinlichkeit von weniger als 0,1% für das Vorhandensein des Haemophiliegens auf. Im übrigen wäre uns bei unseren ausgedehnten Nachforschungen ein Haemophiliefall aus dem Tenner Stamm kaum entgangen, da ein solcher immer Aufsehen erregt

und in der Familientradition behalten oder in den reichlichen Quellen aus den letzten 200 Jahren, die von uns in Graubünden eingesehen wurden, vermerkt worden wäre. Die Haemophiliefälle im weiteren Verwandtenkreis der uns bekannten Probanden wären uns auch sicherlich mitgeteilt worden.

Allerdings konnten bis zu unseren eigenen Untersuchungen die als Kleinkinder vor einer wahrnehmbaren Manifestation des Leidens verstorbenen Träger des Haemophiliegens überhaupt nicht erfaßt werden, wobei uns hier die oberste Altersgrenze von 6 Lebensjahren als angemessen erscheint (vgl. Tab. 13). Das Erfassen von klinisch noch nicht manifest haemophilen Kleinkindern ist erst 1956 durch unsere gerinnungsphysiologischen Untersuchungen möglich geworden (vgl. B XI. 507 im speziellen Teil der Arbeit).

Die bereits erwähnte Berechnung der Wahrscheinlichkeit für das Vorkommen des Haemophiliegens bei den Gliedern eines Bluterstammes von S. ROSIN wird anhand von Beispielen erläutert.

Im Lichte der Ergebnisse unserer Nachforschungen kann das Vorkommen von uns unbekannten Seitenlinien der Bluter von Tenna abgelehnt werden; eine gemeinsame Abstammung mit den Blutern im Sernftal, Glarus (vgl. Tafel 3), ist als zweifelhaft zu bezeichnen. Der Bluter A IX. 10, dessen haemophile Vererbung aus dem Tenner Bluterstamm nicht nachgewiesen werden konnte, scheint auf jeden Fall von keiner unbekannten Seitenlinie abzustammen (vgl. Extratafel 1 zu Nachfahrentafel A, im speziellen Teil der Arbeit). Er wird im Text als «sporadischer Fall» bezeichnet, in der Annahme, daß seine Bluterkrankheit auf einer vom Tenner Bluterstamm unabhängigen Mutation zu Haemophilie beruht.

Über etwaige haemophile Vorfahren des ersten bekannten Stammelternpaares des Tenner Bluterstammes gibt es keine Quellenangaben oder Nachrichten. Wir müssen die Frage offen lassen, ob Ursula BUCHLI (II.3) bereits haemophile Vorfahren hatte; andernfalls wäre die Mutation bei ihr erfolgt, was wir nach den von uns (siehe S. 55 ff.) angestellten Überlegungen für wahrscheinlicher halten. Wir können demnach (mit einiger Sicherheit) annehmen, den ganzen Bluterstamm von Tenna mit den 55 erblichen Blutern vollständig erfaßt zu haben.

Das vorhandene Material wird für die Angaben über Fertilität und Sterblichkeit im Tenner Bluterstamm ausgewertet.

Die im Teil A unserer Nachfahrentafel aufgeführten Personen sehen wir als eine möglichst ideale Vergleichsbevölkerung an, da sie, ohne die haemophile Vererbung aufzuweisen, den Personen aus den Bluterfamilien aus den Teilen B und C der Nachfahrentafel in Abstammung, Lebensweise, sozialer

Stellung und Kulturkreis gleichen. Die Fertilitäts- und Sterblichkeitsverhältnisse im Bluterstamm von Tenna werden in den Tabellen 6, 7, 8, 9, 10, 11 und 12, Tafel 5 (im Anhang) und in den Figuren 2 und 3 angegeben. Für die Berechnung des Selektionsnachteiles anhand der von uns hier zusammengestellten Angaben wird auf die Arbeit von ROSIN, MOOR-JANKOWSKI und SCHNEEBERGER (1958) verwiesen. Es kann aber schon hier vermerkt werden, daß für den Tenner Bluterstamm der Selektionsnachteil der erhöhten Sterblichkeit der Bluter durch eine größere Kinderzahl in den Bluterfamilien aufgewogen zu sein scheint.

Im Hinblick auf die Möglichkeit einer X-chromosomalen Koppelung wurden 52 Personen aus den Bluterfamilien, darunter alle 11 in der Schweiz lebenden Bluter, einer Farbsinnprüfung mittels der ISHIHARA-Tafeln unterzogen. Es wurde dabei keine sichere Farbensinnanomalie festgestellt. Von den so untersuchten Personen wurden auf Anregung von A.E. MOURANT 50 Probanden, darunter 9 Bluter, auf das CN-Geruchssinnempfinden nach der von ALLISON (1953) beschriebenen Methode, sowie mit einem Kontrolltest geprüft. Die Resultate sind nicht leicht zu interpretieren. Jedenfalls geht der Erbgang einer CN-Geruchssinnanomalie im Stamm der Bluter von Tenna nicht parallel mit der Vererbung des Haemophilie B-Gens. Für detaillierte Angaben über diese Untersuchungen wird auf die Arbeit von HUSER, MOOR-JANKOWSKI, TRUOG und GEIGER (1958) verwiesen.

Aus dem Gang der Nachforschungen und Untersuchungen hat sich die Darstellungsweise unserer Resultate ergeben, auf deren eingehende Beschreibung hier nur verwiesen werden kann, da sie in der Zusammenfassung keinen Platz findet.

Die sich aus dem zusammengestellten Material ergebenden Probleme werden in der abschließenden Diskussion besprochen.

Die von BRINKHOUS und GRAHAM (1954) für die Haemophilie A postulierte erbmäßige familiäre Verankerung der milden und schweren Krankheitsformen wird von uns auch für die Haemophilie B angenommen. Sie äußert sich bei den Tenner Blutern vor allem in der Konstanz des Faktor IX-Mangels, der bei allen 10 gerinnungsphysiologisch untersuchten, zum Teil nur sehr weit verwandten Blutern, in der engen Grenze von 2,5 bis 6% der Norm liegt, welcher Befund blutchemisch einer mittelschweren Form der Haemophilie entspricht. In Anbetracht dieser quantitativen, erbmäßigen Verankerung des Faktor IX-Mangels in einem weitverzweigten Bluterstamm und in Kenntnis anderer Fälle von Haemophilie B mit verschiedener Ausprägung des Faktor IX-Mangels, möchten wir, in Anleh-

nung an die von BRINKHOUS und GRAHAM (1954) für die Haemophilie A postulierte Allelserie, auch für die Haemophilie B eine Allelserie annehmen (vgl. S. 82). Es ist denkbar, daß die beiden Serien, wie von VOGEL (1955a) vorgeschlagen, im Verhältnis der Pseudoallelie zueinander stehen.

Im Gegensatz zu den gerinnungsphysiologischen Befunden ist die Einheitlichkeit der klinischen Erscheinungen bei den Tenner Blutern weit weniger eindeutig. Es kann zwar im allgemeinen, auf den ganzen Bluterstamm bezogen, auch von einer klinisch mittelschweren Form der Erkrankung gesprochen werden: es treten fast alle Blutungsarten und oft in starker Ausprägung auf; sie sind jedoch nicht sehr häufig, selten spontan, schließen in keinem Fall physische Betätigung und Ausüben von manuellen Berufen aus und hinterlassen meist keine schweren bleibenden Folgen. Dennoch kann nur sehr bedingt von familiärer Übereinstimmung der Blutungsmerkmale gesprochen werden, da in der Ausprägung der klinischen Erscheinungen beträchtliche individuelle Unterschiede festzustellen sind. Neben Fällen mit fast gleichmäßigem Auftreten aller Blutungsarten treffen wir auch solche, bei welchen trotz verhältnismäßig starker Blutungserscheinungen die eine oder andere sonst charakteristische haemophile Blutungsart wie Nasenbluten, Blutungen aus dem Mund oder Suffusionen, vollständig fehlt (vgl. Tab. 13). Der zeitliche Beginn der klinischen Erscheinungen weist, trotz meist sehr ähnlicher Umweltsbedingungen, ebenfalls eine große Variationsbreite auf, die vom 1. Lebensjahr bis zur Pubertät reicht.

Als ein Beispiel der individuellen Unterschiede im klinischen Krankheitsbild kann hier der klinisch einwandfrei nicht manifeste jugendliche Proband B XI. 507 und sein schwer manifester Bruder B XI. 505, beide mit 2,5% an Faktor IX, erwähnt werden.

B XI. 507 stellt somit den Fall eines nicht manifesten Bluters mit einem ausgesprochen haemophilen Laboratoriumsbefund dar.

Auch das Abklingen der Blutungserscheinungen mit dem Alter, auf welches noch ausführlich eingegangen wird, zeigt beträchtliche individuelle Unterschiede in der Ausprägung und im zeitlichen Auftreten.

Es ist denkbar, daß die individuellen Unterschiede im klinischen Krankheitsbild, innerhalb des gleichen Bluterstammes und bei gleichen Faktor IX-Mangelwerten, auf erbmäßig verankerte konstitutionelle Differenzen zurückzuführen sind.

Wie bereits erwähnt, kann bei den Tenner Blutern die Abnahme oder sogar ein vollständiges Abklingen der Blutungserscheinungen mit dem Alter festgestellt werden, und zwar bei weiterbestehendem Faktor IX-Mangel im Blute. Wir begegnen damit erneut Fällen von nicht manifesten Blutern mit haemophilen Laboratoriumsbefunden.

Die Abnahme der Blutungserscheinungen mit dem Alter ist bei den Tenner Blutern auch aus der früheren Literatur zu entnehmen. Ähnliche Beobachtungen wurden an ihrem Material von SCHLOESSMANN (1930) und ANDREASSEN (1943) gemacht.

Eine Erklärung für dieses Verhalten ist uns nicht bekannt, auch hier könnten jedoch unbekannte blutchemische Faktoren oder Gefäßkomponenten mitbestimmend sein.

Ähnlich wie GRANDIDIER (1877), SCHLOESSMANN (1930) und DEUTSCH (1954) in ihrem Beobachtungsgut, fanden wir auch bei den Tenner Blutern einige Fälle von jahreszeitlichen Schwankungen der haemophilen Blutungserscheinungen. Wir versuchen diese anhand unserer Beobachtungen als konstitutionell bedingte Klima- bzw. Jahreszeitempfindlichkeit zu erklären, welche bei den Blutern durch die vorhandene Gerinnungsstörung eine besondere klinische Ausprägung erhält.

In die Kategorie der konstitutionell bedingten Einflüsse auf die Steigerung der Blutungserscheinungen könnte ebenfalls die bei Föhnwetter, Aufregung oder Indisposition verstärkte Blutungstendenz bei zwei Tenner Blutern gerechnet werden.

Es konnten zahlreiche Fälle von *charakteristischen haemophilen Nachblutungen* bei den Tenner Blutern beobachtet werden, wie sie bereits für sein Material von GRANDIDIER (1855a) beschrieben und von SCHLOESSMANN (1930) und neuerlich von DEUTSCH (1954) genauer definiert worden sind. Diese für die Haemophilie pathognomonische Erscheinung ist unseres Wissens bis jetzt unerklärt geblieben. Wir nehmen an, daß sie mit einer noch unbekannten Gefäßkomponente oder auch mit einem noch nicht erfaßten blutchemischen Faktor zusammenhängen kann.

Aus der Übersicht der bisherigen Literatur ergibt sich, daß die Frage der abnormalen Blutungserscheinungen bei heterozygoten Konduktorinnen nicht endgültig abgeklärt ist.

Unserer Ansicht nach kann nur eine generalisierte Blutungstendenz mit entsprechendem Laboratoriumsbefund, ähnlich wie bei männlichen Blutern und homozygoten weiblichen Bluterinnen, wenn auch in leichterer Ausprägung, als eine Blutungsbereitschaft bei heterozygoten Konduktorinnen bewertet werden. Im Gegensatz zu der Annahme von DEUTSCH (1954) scheint es uns, daß Neigung zu einer einzelnen Blutungsart, sei es zu Menorrhagie, oder zu Suffusionen, oder auch zu Nasenbluten, schon in Anbetracht der starken Verbreitung dieser Blutungserscheinungen bei der normalen Bevölkerung nicht als Beweis der haemophilen Blutungstendenz angesehen werden kann. Auch scheint es uns nicht gut denkbar, daß das gleiche Gen, welches die bei jedem Haemophiliefall feststellbaren multiplen Blutungsarten bedingt,

bei den heterozygoten Konduktorinnen nur die Neigung zu einer einzelnen Blutungsart hervorrufen würde.

Es wird vor der Überwertung der einfachen Gerinnungszeitbestimmung gewarnt, die, abgesehen von den vielen kaum vermeidbaren Fehlerquellen, auch eine große physiologische Variationsbreite aufweist. Wir betrachten es deshalb nicht als angängig, wenn HALDANE (1946/47) die von ANDREASSEN (1943) beschriebene leichte Gerinnungszeitverlängerung bei den von ihm untersuchten weiblichen Heterozygoten als «physiologischen Nachweis» des Haemophiliegens auslegt und sie für seine Berechnungen der Mutationsrate mitverwendet.

Immerhin sollten die Angaben mehrerer Autoren über die Konduktorinnen mit Blutungserscheinungen, zum Teil auch multipler Art, nicht übergangen werden. Nachdem nun *das Fehlen jeglicher mit den heutigen Mitteln erfaßbaren Blutungsbereitschaft bei den heterozygoten Konduktorinnen aus dem Tenner Bluterstamm mit mittelschwerer Form der Haemophilie B* festgestellt wurde, sollten auch bei Bluterstämmen mit anderen Formen der Haemophilie klinische und gerinnungsphysiologische Untersuchungen durchgeführt werden.

Summary

The Hemophiliacs of Tenna are named after the Walser colony in the Grisons (Switzerland), where the first-known hemophiliacs of this kindred can be traced back to the 17th century. It is justified to consider the Walser population of Tenna and the neighbouring settlements of Safien and Versam as homogenous and the whole region as a relative isolate (IKIN, MOURANT, KOPEĆ, MOOR-JANKOWSKI and HUSER, 1957; MOOR-JANKOWSKI, HUSER and ROSIN, in preparation). The population has undergone very little change since the 14th century (Joos, 1946), and migrations were nearly exclusively emigrations (cf. Tab. 2), mostly to the surrounding valleys. The descendants of the first-known ancestral parent couple of the Tenna Hemophiliacs in their majority still live at Tenna or in its vicinity (see map p. 1 and Tab. 1). The geographical distribution of the known Tenna hemophiliacs roughly corresponds to that of the non-hemophilic population; hemophilia, under the local conditions, constituted an additional reason for emigration.

A considerable number of studies have already been written on the Tenna Hemophiliacs. All the original descriptions (THORMANN, 1837; VIELI, 1846; GRANDIDIER, 1855a and 1877; HOESSLI, 1885; HOESSLY-HAERLE,

1930, and PIANTA, 1953) and the more important compilatory works (BULLOCH and FILDES, 1912; SCHLOESSMANN, 1930, and FONIO, 1954) are thoroughly discussed and the errors and misapprehensions corrected on the ground of archival sources and most recent research work.

There is conclusive evidence in early descriptions of the first half of the 19th century that hemophilic heredity and the typical bleeding phenomena were well known at Tenna at that time. The people of Tenna are among the first to have used the German term “Bluter” for bleeder, and their expression “Conductor” for the female transmitter of the gene was adopted by GRANDIDIER (1855a) and introduced into the pertaining literature.

The point of departure for this study were the Church Registers, Civil Registers and archives of a great number of villages and towns, in order to compile the most complete possible descendants' table of the first-known ancestral parent couple of the Tenna Hemophiliacs: Albrecht WALTHER, II.2, and Ursula BUCHLI, II.3, who lived in the middle of the 17th century.

The methods employed in the genealogical investigation are described in detail and so are the particularities of the Swiss citizenship, mostly unknown to foreigners, which have greatly facilitated our research work.

All male and female Swiss are hereditary citizens of a commune (“Heimat-gemeinde”), which need not coincide with their place of birth or residence. The citizenship is handed down in the male ancestors' line; when marrying, the wife assumes the citizenship of her husband; illegitimate children, who are not recognized by the father receive the citizenship of the mother; foreigners acquire first the citizenship of a commune, and on the ground of this citizenship become Swiss nationals.

The Swiss citizenship has at all times bestowed certain advantages attached to the respective commune, such as – among other things – the right to be supported in case of need or old age and shares and usufruct in the property of the commune, viz. forests, commons and Alpine pastures (cf. P. LIVER in ZÜRCHER, 1957). This unique institution and the privileges it implies accounts for the care with which all pertaining documents and deeds have been preserved through centuries.

In 1860, all Grisons communes introduced Citizens Registers. They contain particulars about birth, marriage and death of all the citizens of the commune. As prescribed by the law, these Registers are kept with a high degree of accuracy by the Civil Registrars and thus constitute, together with the archival records, a reliable source for genealogical research work.

The total number of persons genealogically recorded is contained in Tab. 3. The Descendants' Table lists bleeders and persons with possible hereditary hemophilia down to the end of 1956 and to the middle of 1957, respectively; other recorded persons down to the end of 1955. *The bleeders and hemophilic families, however, were only found out from among the persons recorded in the Descendants' Table, after the latter was completed down to 1955, so all the descendants, whether hemophilic or not, were followed up with the same care.*

The scope of investigation regarding the descendants of the ancestral parent couple can be seen from Tab. 4: among 3072 descendants and their spouses, 115 persons, mostly in younger generations and without children, could not be followed any further owing to the lack of available information. Such persons were labelled "recorded at birth, but intraceable thereafter" in the text and in Tab. 4. In addition, 108 persons belonging to younger generations were not followed any further when we closed our lists. They were mostly women married to foreigners, whose follow up would have involved major difficulties without, however, changing the results to any appreciable extent. They were designed in the text and in Tab. 4 as "recorded at birth, but follow-up discontinued through close of investigation".

The bleeders in the Descendants' Table were ascertained by means of a specially conceived questionnaire. All possible carriers of the Tenna hemophilia gene, living in Switzerland at the time of investigation, i.e. the great majority of the possible carriers, were submitted to clinical examination according to our questionnaire, which, in most cases, was supplemented by coagulation tests.

Among those descendants of the Tenna Hemophiliacs who had died before the onset of our investigation, those were considered hemophilic who, in the contemporary sources, were designed as such or as having bled to death. In view of the fact that already at the beginning of the 19th century, the hemophilic syndrome was incontestably well-known at Tenna, this point of view seemed justified.

Basing on contemporary reports and our own investigations, we reject the atypical hemophilic heredity and the existence of "rudimentary bleeders" among the Tenna Hemophiliacs, as was claimed by HOESSLY-HAERLE (1930).

We likewise reject the existence of hemophilic symptoms in heterozygous carriers of the Tenna Kindred, which was assumed by HOESSLY-HAERLE (1930) and PIANTA (1953). Our respective views are based on contemporary statements and, for more recent times, on our own obser-

ventions covering several years, on repeated clinical tests and laboratory findings in coagulation tests.

Since we considered the determination of the coagulation time in the whole blood as an inaccurate method, we substituted for it fractionate coagulation tests. These were carried out by M. GEIGER at the Coagulation Laboratory of Zurich Kantonsspital (Professor F. KOLLER). They showed in the 10 bleeders who were examined pathological Factor IX values of 2.5 to 6% as compared to standard, which corresponds, as far as coagulation tests are concerned, to a medium degree of hemophilia B.

The still pending question of nomenclature in hemophilia is briefly skirted.

In the coagulation tests on 11 certain, and 33 possible carriers, no coagulation disorder was found. The probability in % for the existence of the hemophilia gene in the possible carriers was calculated by S. ROSIN, and can be seen from Tafel 6.

A comparison of the Factor IX values in the examined bleeders and carriers is contained in the diagram on p. 47.

It may be taken for granted that all Tenna Hemophiliacs living at the time of our investigation were recorded by us, which was greatly facilitated by the fact that we know in person a large number of individuals from this kindred (cf. Tab. 5). From among the 13 bleeders living in the period of 1952-1956 we could personally submit 11 to clinical examination and record the examination results of the treating family doctors (whom we also knew) and the hospitals. For the 2 bleeders B IX. 323 and B XI. 472, who live in the United States, we had to limit ourselves to information from their nearest relatives. 10 bleeders could be submitted to coagulation tests.

We also assume that we covered most of the Tenna Hemophiliacs who have died before this study was started. Greater uncertainty regarding the degree of covering all Tenna Hemophiliacs only exists for the time before 1790: for that period, entries in Church Registers only, but no medical descriptions were available. However, there were only few cases of hemophilia theoretically possible among the Tenna Kindred of that time; they are all listed in Tafel 2 and provided with ratings of probability in % for the existence of the hemophilia gene by S. ROSIN. After 1790, the inventory of the Tenna Hemophiliacs may be considered as nearly, and from 1840 as virtually complete. The probability of hemophilic descendants of the 108 persons who were "recorded at birth, but whose follow-up was discontinued at close of investigation" was calculated by S. ROSIN and is contained in Tafel 1. The possibilities for the existence of such unknown hemophilic descendants is, however, extremely small, for the persons

"recorded at birth, but untraceable thereafter" were mostly childless and for that very reason untraceable; and the persons "recorded at birth, but follow-up discontinued at close of investigation" show a probability of less than 0.1% for the existence of the hemophilia gene. Apart from this, a case of hemophilia among members of the Tenna Kindred could hardly have escaped our extensive investigations; such a case always causes sensation; it would have been remembered in the family tradition or recorded in the abundant sources from the past 200 years, which we had access to in the Grisons. Also should we have undoubtedly been informed about cases of hemophilia among the distant relatives of the persons examined by us.

It must be admitted, however, that carriers of the hemophilia gene, who, up to the beginning of our investigation, had deceased as infants before the trouble became discernably manifest, could not be covered at all; it seemed appropriate to put an upper age limit of 6 years for such cases (cf. Tab. 13). The recording of clinically not-yet manifest hemophilic infants has only become possible in 1956 thanks to our coagulation tests (cf. B XI. 507 in the Special Part of the study).

The afore-mentioned calculation of the probability of the existence of the hemophilia gene in the members of a kindred of hemophiliacs has been supplied by S. ROSIN and is illustrated with examples.

In the light of our investigations and their results, the existence of unknown side-lines of the Tenna Hemophiliacs can be rejected; the common descentance with the bleeders in the Sernf Valley, Canton of Glaris (cf. Tafel 3) is to be considered as doubtful. Bleeder A IX. 10, whose hemophilic heredity from the Tenna Kindred could not be proved, does in any case not seem to stem from an unknown side-line (cf. Extra Tafel 1 to Part A of Descendants' Table, in the Special Part of the study). He is designated as "sporadic case" in the text, assuming that his hemophilia was caused by a mutation independent of the Tenna Kindred.

As regards the possible hemophilic ancestors of the first-known ancestral parent couple of the Tenna Hemophiliacs, the lack of sources forbids to make any allegations. Our considerations seem to point against such a possibility, so that we assumed to have completely covered the Tenna Hemophiliacs Kindred with the 55 hereditary bleeders that we recorded.

The available material was evaluated by us as to statements on fertility and mortality among the Tenna hemophiliacs.

The persons contained in Part A of our Descendants' Table were considered ideal for the purpose of comparison, since they resemble the members of the hemophilic families in Parts B and C of the Descendants'

Table as to extraction, way of life, social standing, and cultural environments, yet had no hemophilic heredity. The fertility and mortality in Tenna Hemophiliacs are shown in Tables 6, 7, 8, 9, 10, 11 and 12, in Tafel 5 (of the Appendix), and in Figs. 2 and 3. For the calculation of the disadvantage in selection on the basis of the facts compiled in this study, we refer to the study by ROSIN, MOOR-JANKOWSKI and SCHNEEBERGER (1958); it may be anticipated that, as far as the Tenna Hemophiliacs are concerned, the selectional disadvantage of the increased mortality of the bleeders seems to be counterbalanced by a higher number of children in hemophilic families.

In view of the possibility of linkage in the X-chromosome, 52 persons from the bleeders' families, and among them all the 11 bleeders living in Switzerland, were submitted to tests for colour-blindness by means of the ISHIIHARA Tables. No sizeable visual disorder as to colours could be established. Following a suggestion by A. E. MOURANT (1950), 50 persons among whom 9 bleeders, all chosen from among the above-mentioned test persons, were further examined for their ability to smell potassium cyanide. For details of these tests we refer to the study by HUSER, MOOR-JANKOWSKI, TRUOG and GEIGER (1958).

The following outline is a summary of the detailed description of the presentation of our material.

The General Part of the study describes the recording procedures and the compiling and evaluation of the material. The subsequent Special Part contains the description of all the cases that are of interest for hemophilic heredity or that were submitted to coagulation tests or that gave otherwise raise to discussion.

The total of 3072 recorded members of the Tenna Kindred and their spouses is contained in the Descendants' Table of the first-known ancestral parent couple. To make the presentation easier to survey, the Table was subdivided into 3 parts (Parts A, B, and C), which, together with 2 handier excerpts (Tafel 5 and 6), are to be found in the appendix.

All persons listed in the Descendants' Table or its extracts have a location number. This number will enable the reader to find, in the Special Part of the study, all the cases that gave raise to discussion and, in the Register of Names, the particulars of all the persons recorded.

Consecutive Numbering of Each Person:

Each person carries an Arabic numeral. The numbering within each generation is consecutive. It always starts in Part A of the Descendants' Table and continues into Parts B and C. By way of supplement, the Arabic numerals are occasionally provided with additional small letters, e.g. 31a, 31b; furthermore, the descendants, added by way of supplement, of the parent couple B VI. 35, B VI. 36 were marked from the VIIIth generation in the Descendants' Table with an additional numbering in Arabic numerals provided with *, starting in each generation with 1, e.g.: 1*, 2*, 3*... etc. All supplementary numbers are copied out for each generation at the end of each part of the Descendants' Table, in order to reduce the sources of error in counting out.

The supplements were merely caused by technical consideration while completing the Descendants' Table: they were introduced when the recorded facts were completed. *The supplementary items, however, are in no way different from the other items of the Descendants' Table.*

The persons listed in the Descendants' Table are usually recorded in the order of their birth dates. In several instances, however, this order could not be maintained for reasons of clear representation or owing to subsequent supplements.

In the Excerpts from the Descendants' Table (Tafel 5 and 6), the grouping in the order of birth dates was maintained without exception. This caused some shifts in the order of location numbers, e.g. in Table 5, IVth generation, location number 19 stands before number 10.

The individual numbers of the consecutive numbering in Arabic numerals in the Descendants' Table are copied out in the following cases only:

- the first and last numbers of each generation in Parts A, B, and C
- every tenth number
- the numbers of the persons discussed in the text; these numbers are underlined in the Descendants' Table
- each person that occurs more than once, their location numbers in the Descendants' Table being written in full every time
- all supplement numbers, whether with small letter or with *
- the number preceding each supplement number

References in the Descendants' Table:

Persons mentioned more than once in the Descendants' Table are provided with references to their other location numbers. The following cases are possible:

- reference to the same person in the same generation of the same part of the Descendants' Table, e.g. in Part A, IXth generation, 20, 130
- reference to the same person in another generation of the same part of the Descendants' Table, e.g. in Part B, Xth generation, 266, XI, 512
- reference to the same person in another part of the Descendants' Table, e.g. in Part A, IXth generation, 67, B IX, 335

In references to persons discussed in the text, only the location number under which the person is discussed is underlined, e.g. in Part C, VIIth generation, 184, B VI. 106, i.e. the person is dealt with in the text under number B VI. 106.

Further details on the references are contained in the explanation to the Descendants' Table.

Marriages in which the ancestors of both partners are listed in the Descendants' Table, can be traced back to common ancestors and are thus consanguine. Hence all marriages with reference numbers (see below) are consanguine. Where the consanguinity is evident direct from the Descendants' Table, the persons were recorded only once with their reference numbers, e.g. in A VII. 8 copulated with A VII. 9.

However, the Descendants' Table also contains a number of consanguine marriages that cannot be recognized as such from the Descendants' Table, their common ancestors not being recorded there, as they did not belong to the Kindred of Tenna. Thus the proportion of consanguine marriage in the Descendants' Table is considerably larger than can be seen from this presentation. This is not surprising as the population under discussion for the greater part originates from the typical endogamous parts of the Grisons (cf. pp. 5-10 and Tab. 1).

The Register of Names:

The Register of Names contains the particulars of all the 3072 persons covered by this study. In addition, the names of the persons contained in Tafel 4 are recorded.

The Register of Names was edited by G. TRUOG, M. SCHNEEBERGER and J. K. MOOR-JANKOWSKI from the Institut de Génétique Médicale (Dr. D. KLEIN), Clinique Universitaire d'Ophthalmologie, Geneva (Director: Prof. A. FRANCESCHETTI).

The Register of Names is not published; a copy of it was given to a number of Swiss and foreign institutes whose addresses are listed on p. 78 of the study.

One copy can be obtained on loan from the Institut de Génétique Médicale in Geneva, Switzerland. Other institutes will apply their own regulations.

The Register of Names is considered a manuscript and is to be used under observance of the customary secrecy of the medical profession.

The following abbreviations were used in the Register of Names as well as in the description of the cases in the General and the Special Parts of the study:

- K. = Church Register (Parish register, register of marriages and deaths)
- Z. = Civil Registrar's Register
- E. = Register of Inhabitants
- T. = Tenna
- S. = Safien (i.e. Safien-Platz, Safien-Neukirch, Safien-Thalkirch)
- Ve. = Versam
- Val. = Valendas
- P. = Known to us in person as patient
- P.v.T. = Known to us in person as patient and citizen of Tenna (or, analogously, of S., Ve., Val.)
- pers. M. or P. M. = Personal communication
- ... = Particulars missing

Date of birth marked †, e.g. 1731 † = Deceased shortly after birth

† before date of death, e.g. † 1684 = Only date of death known

The Register of Names is subdivided in the order of generations. Within each generation, the particulars for Parts A, B and C of the Descendants' Table are separated from one another by red lines. The recorded persons are classified by their location numbers in the Descendants' Table; persons mentioned more than once show all their location numbers. Married couples are represented with a bracket for copulation.

The following particulars are stated of each person:

Location number	Christian name	Name	Year of birth ¹⁾	Year of death ¹⁾	Year of copulation	Source
		"Native Commune" ²⁾ (Heimatgemeinde)		Residence ³⁾ and remarks		

Where particulars are missing, they could not be found in the original sources.

¹⁾ All statements taken from Church Registers dating back further than 1837 show, instead of the dates of birth and death, those of baptism and burial, respectively. The

inaccuracies thus caused are irrelevant, as it was custom in the Grisons to baptize the new-born children within a few days after birth.

²⁾ For deceased persons whose native commune ("Heimatgemeinde") is not stated, the village or town where they were registered in the Parish Register or in the Civil Register as a rule co-incides with the native commune.

³⁾ Where the Registers of Inhabitants are quoted, the persons in question are resident at the place of the Register.

A sample page of the Register of Names is shown in Fig. 4, p. 79.

The problems arising from the compiled material are taken up in the conclusive Discussion.

The familiar heredity of mild and severe forms of hemophilia A, which was postulated by BRINKHOUS and GRAHAM (1954), is, in our opinion, also to be assumed for hemophilia B. In the Tenna Hemophiliacs it is notably manifest in the constant quantitative deficiency of Factor IX. All the 10 hemophiliacs – partly only very distantly related to each other – who were submitted to coagulation tests, showed Factor IX contents between the narrow limits of from 2.5 to 6% of normal. This corresponds, as far as coagulation tests are concerned, to a medium-severe form of hemophilia. In view of this quantitative hereditary expression of Factor IX deficiency within a wide-branching kindred of hemophiliacs, and in the light of cases of hemophilia B with various Factor IX deficiencies that were described by other authors, we would, as BRINKHOUS and GRAHAM did for hemophilia A (1954), also *assume an allele series for hemophilia B* (cf. p. 82). Possibly, the two series, as was suggested by VOGEL (1955a), are related to one another as pseudoalleles.

In contrast to the findings in the coagulation tests, the clinical symptoms in the Tenna Hemophiliacs are much less consistent and conclusive. In general, and referring to the whole kindred of bleeders, it seems justified to speak likewise of a clinically medium-severe form of hemophilia. The hemophiliacs exhibit all types of bleeding, yet, bleedings are mostly not very frequent, rarely spontaneous, and in no instance exclude physical activities or the pursuit of manual occupations; they generally leave no severe and lasting sequels. Notwithstanding there is only a relative familial concordance of the clinical symptoms, which show considerable individual variations. Apart from cases with a virtually equal frequency of all types of bleeding, we also encountered cases that were characterized by comparatively strong bleeding symptoms in general, but showed the complete absence of otherwise typical hemophilic phenomena such as nose-bleeding, bleeding from the mouth, or suffusions (cf. Tab. 13). In spite of mostly very similar surroundings, the onset of clinical phenomena varies a great

deal and may lie between the first year of life and puberty. For an example of such individual differences we refer to two brothers who grew up under identical conditions: One of them, B XI. 505, has been suffering from multiple bleeding phenomena since his first year, *whereas the other, B XI. 507, who was repeatedly examined by us in the years 1956–1957, has not shown any disposition to bleeding up to this present fifth year, although the findings of his coagulation tests of 2.5° of Factor IX are identical with those of his manifestly hemophilic brother. Thus, B XI. 507, represents a case of hemophilia with no clinical symptoms.*

The abatement of hemophilic phenomena with age, which is dealt with in greater detail below, also shows considerable individual differences as to degree and onset.

The individual differences in the clinical picture of the disease within the same kindred of bleeders with constant quantitative Factor IX deficiency, might be caused by hereditary differences in constitution; this question ought to be cleared up more exactly.

As was already mentioned, *an abatement or even complete recession of hemophilic phenomena with age by persistent Factor IX deficiency could be observed among the Tenna Hemophiliacs.* Similar observations were already made by SCHLOESSMANN (1930) and ANDREASSEN (1943) and, among the Tenna Hemophiliacs, by HOESSLY-HAERLE (1930). We know of no explanation for this phenomenon; here, too, chemical factors in the blood, unknown as yet, or a vascular component, may be of decisive influence.

Similarly to GRANDIDIER (1877), SCHLOESSMANN (1930), and DEUTSCH (1954), we also encountered among the Tenna Hemophiliacs some cases of seasonal fluctuations in the hemophilic bleeding phenomena. An explanation is attempted on the grounds of our observations on Hemophiliac C XI. 648, who for the past 10 years has not suffered any more of hemophilia. In his youth, the subject had had severe, persistent nose-bleeding every day in spring and in autumn. Since his hemophilia has come to a stop, he still suffers of frequent, though not severe and persistent, nose-bleeding in the spring and in the autumn. Rhinorrhagia within "normal" limits is, however, frequently found in persons without any coagulation disorder; the seasonal increase may be caused by a frequently encountered constitutional sensitivity to climate or season, which, in bleeders, becomes particularly distinct and clinically manifest through the existant coagulation disorder.

Also to be reckoned to the category of constitutionally caused increases in the hemophilic phenomena is the intensified disposition to bleeding in

"föhn" weather ("föhn" = warm, dry wind in Alpine regions). in commotions or ill health, which we observed in two Tenna Hemophiliacs.

We observed many cases of *characteristic secondary hemorrhage* ("Nachblutung") in Tenna Hemophiliacs. This phenomenon, which is almost pathognomonic for hemophilia, has, to our knowledge, not been explained by the most recent achievements of coagulation research. We assume that it may be connected with a chemical factor in the blood as yet unknown or with an *unknown vascular component in hemophilia*.

It follows from the review of the hitherto existing literature that the question of abnormal bleeding phenomena in heterozygous carriers has not found a final answer.

In our opinion, only a generalized tendency for bleeding with corresponding laboratory findings – similar to male hemophiliacs and homozygous female bleeders – may be considered as hemophilic disposition in heterozygous carriers, though its form will be slighter. In contrast to what was put forward by DEUTSCH (1954), we believe that a disposition to a single kind of bleeding such as menorrhagia, nose-bleeding, suffusions, etc. must not be considered as evidence for hemophilic bleeding tendencies, since such bleeding phenomena are wide-spread among normal people. Also, it seems hardly probable that the same gene which provokes the multiple types of bleeding in every case of hemophilia, should only cause the disposition to one single type of bleeding in heterozygous carriers.

We would also warn against over-estimating the mere determination of coagulation time. This method not only involves a great number of hardly avoidable sources of error, but the coagulation time itself shows a large range of physiological variation. We can therefore not agree with HALDANE (1947), who considers the slight prolongation of the coagulation time in heterozygous females described by ANDREASSEN (1943) as "physiological evidence" for the existence of the hemophilia gene and, what is more, employs this "evidence" for his calculations of the mutation rate of hemophilia.

Nevertheless the reports of several authors referring to carriers with, partly, multiple bleeding phenomena should not be neglected. Any bleeding disposition in the heterozygous carriers among the Tenna Hemophiliacs with a medium-severe form of hemophilia B has now, with the methods available, been proved to be absent; clinical and coagulation tests should now also be carried out with hemophilic kindreds showing other forms of hemophilia.

II. Spezieller Teil*

1. Gemeinsame Vorfahren der drei Stämme aus den Teilen A, B und C der Nachfahrentafel

- I. 1: Samuel WALTHER, Ammann, von Tenna, geb. um 1600,
† 67jährig 1667 (K.T.), kopuliert mit
- I. 2: keine Personalangaben bekannt.

- II. 1: Verena BUCHLI, von ?, geb. ?, † ? (K.T.),
nicht eheliche Verbindung mit
- II. 2: Albrecht WALTHER, Ammann, von Tenna, † 36jährig 1684
(K.T.), kopuliert 1669 mit
- II. 3: Ursula BUCHLI, von ?, † 1681 (K.T.).
II. 2 und II. 3 können, ohne nähere Angaben über sie selbst, als
das erste bekannte Stammelternpaar der Bluter von Tenna ange-
sehen werden. da ihr Sohn (III.7) der erste bekannte Bluter und
ihre Tochter (III.10) die erste bekannte Konduktorin sind.

- III. 1: Barbara, geb. 1668. † ?, uneheliche Tochter von II. 2 und II. 1
(K.T.).
- III. 2: Samuel WALTHER, von Tenna, geb. 1670, † 1671 (K.T.).
- III. 3: Martin HUNGER, von Safien, † 85jährig 1746 (K.S.), siehe un-
ter Teil A, kopuliert 1692 mit
- III. 4: Barbara WALTHER, von Tenna, geb. 1672, † 1746 (K.T. und
K.S.), siehe unter Teil A.
- III. 5: Totgeburt 1675 (K.T.).
- III. 6: Maria JUON, von Safien, † 1712 (K.T.), siehe unter Teil B,
kopuliert 1701 als erste Frau mit
- III. 7: Samuel WALTHER, Ratsherr, von Tenna, geb. 1676, † 1741
(K.T.), siehe unter Teil B, kopuliert 1713 in zweiter Ehe mit
- III. 8: Anna GREDIG, von Safien, † 1749 (K.T.), siehe unter Teil B.
- III. 9: Hans GARTMANN, von Tenna, † 73jährig 1728 (K.T.), siehe
unter Teil C, kopuliert 1694 mit

* Erklärung der Darstellungsweise und der Abkürzungen siehe S. 75 ff.
In petit: Diskussionsfälle aus früherer Literatur.

- III. 10: Ursula WALTHER, von Tenna, geb. 1678, † 1757 (K. T. und K. S.), siehe unter Teil C.
- III. 11: Anna WALTHER, von Tenna, geb. 1681, † 1682 (K. T.).
Von den fünf lebendgeborenen Kindern des Stammelternpaares II. 2 und II. 3 haben nur drei Nachkommen hinterlassen, die übersichtshalber wie folgt zusammengestellt sind:
- III. 4: Barbara WALTHER und ihre Nachkommen im Teil A,
III. 7: Samuel WALTHER und seine Nachkommen im Teil B,
III. 10: Ursula WALTHER und ihre Nachkommen im Teil C.

2. Nachfahrentafel Teil A

- A III. 4: Barbara WALTHER, von Tenna, geb. 1672, † 1746 (K. T. und K. S.)
kopuliert 1692 mit A III. 3 Martin H., von Safien, † 85jährig 1746 (K. S.).
HOESSLY-HAERLE, S. 344–346, bezeichnet die Proposita A III. 4 als Konduktorin, mit der Begründung, daß unter ihren Nachkommen Bluter und «Teilbluterinnen» mit zum Teil «atypischem Erbgang» aufgetreten sind (vgl. diese Nachkommen hier weiter unten im Teil A der Nachfahrentafel). Wir können uns dieser Annahme nicht anschließen und betrachten die Proposita A III. 4 nicht als Konduktorin.

Literaturangaben: HOESSLY-HAERLE, S. 343–347.

- A IV. 1: Albrecht H. von Safien, † 1776 (K. S.)
kopuliert 1739 mit A IV. 2 Ursula BANDLI, von Safien, geb. 1722, † 1788 (K. S.).

Entgegen der Annahme von HOESSLY-HAERLE, S. 344–346, kann der Propositus A IV. 1, nur auf Grund seiner vermeintlichen Bluternachkommen (vgl. weiter unten, Teil A), nicht als «fraglicher Bluter» bezeichnet werden. Für ihn selbst sind keine Anhaltspunkte für Haemophilie zu eruieren und für seine Nachkommen kein Blutererbgang bekannt.

Literaturangaben: HOESSLY-HAERLE, S. 344–346.

- A VII. 7: Alexander H., von Safien, geb. 1827, † 1857 (K. S. und Z. S.).

Entgegen der Annahme von HOESSLY-HAERLE, S. 344–346, kann der Propositus A VII. 7 nicht als «rudimentärer Bluter» angesehen werden; die Angabe über das Nasenbluten in der Jugend des A VII. 7, welche durch HOESSLY-HAERLE um 1930 bei dem Großneffen des Propositus erhalten wurde, dürfte nicht als ein genügender Beweis angesehen werden, ebensowenig wie die Annahme einer «Abschwächung des haemophilen Gens bei gleichzeitig atypischem Erbgang», HOESSLY-HAERLE, S. 348, die zur genetischen Beweisführung zugezogen wird. VIELI, der seine Bestandesaufnahme zu Lebzeiten des Propositus durchführte, erwähnt ihn überhaupt nicht, desgleichen auch HOESSLI, der 1877–1878, also 50 Jahre vor HOESSLY-HAERLE, und zu Lebzeiten des Bruders von A VII. 7, das Tal auf Haemophilie untersuchte. Es ist wenig wahrscheinlich, daß den beiden früheren Autoren die Blutungsneigung des Propositus entgangen und erst 50 Jahre nach HOESSLIs Tode durch HOESSLY-HAERLE erfaßt worden wäre. Die haemophile Vererbung läßt sich für den Propositus ebenfalls nicht nachweisen.

Literaturangaben: HOESSLY-HAERLE, S. 344–348.

A VII. 9: Ursula TESTER, von Safien, geb. 1827, † 1861 (K. S. und Z. S.)
kopuliert 1851 mit A VII. 8 Martin H., von Safien, geb. 1824, † 1904
(K. S. und Z. S.).

Entgegen der Annahme von HOESSLY-HAERLE, S. 344–346, kann die Proposita A VII. 9 nicht als «Teilbluterin» angesehen werden nur auf Grund der Tatsache, daß sie bei der fünften Geburt verblutet ist, und weil sie mütterlicherseits von A IV. 1 (siehe dort) abstammt.

Literaturangaben: HOESSLY-HAERLE, S. 344–346.

A VII. 44: siehe B VII. 175.

A IX. 10: Josua H., von Safien, geb. 1882, † 1905 (Z. S.)

Bluter: Häufiges Nasenbluten katamnestisch durch den noch heute lebenden Bruder Albrecht H., A IX. 11. von Safien, geb. 1884, wohnhaft in Safien, uns gegenüber bestätigt. Der Propositus A IX. 10 wurde in seiner Familie als Bluter angesehen. In früher Kindheit und während der Schulzeit ist seine Blutungsneigung nicht auffallend gewesen. Erst nach der Konfirmation (16 Jahre) hat er mehr, meist aus der Nase, geblutet. Der Bruder A IX. 11 kann sich nicht erinnern, daß der Propositus bei akzidentellen Verletzungen besonders stark geblutet oder sonst auffallende blaue Flecken gehabt hat. Er *starb an Verblutung* aus der Nase, nach ungefähr achttägiger Blutung, im Spital «Krankenasyll Sand» in Chur; genauere katamnestische Angaben bzw. Krankengeschichte sind nicht mehr erhältlich.

Es kann bei dem Propositus kein hämophiler Erbgang nachgewiesen werden. Seine von uns in der Extratafel 1 zu Nachfahrentafel Teil A bis in die achte Generation zurückverfolgten Vorfahren mütterlicherseits, mit Berücksichtigung sämtlicher Geschwister, weisen keine bekannten Bluter auf und lassen sich auch nicht auf das Stammelternpaar II. 2 und II. 3 zurückführen. Es muß hier jedoch erwähnt werden, daß alle Angaben über die Vorfahren des A IX. 10 mütterlicherseits, aus den Kirchenbüchern von Safien-Thalkirch und Safien-Platz, wie auch aus dem Bürgerregister der Gemeinde Safien stammen, wo überhaupt keine Eintragungen über Bluter zu finden sind, im Gegensatz zu den Kirchenbüchern von Tenna und Versam. Es sei deshalb schon im allgemeinen dahingestellt, ob in der Gemeinde Safien, trotz den mehrfachen Familienverbindungen zu Tenna und Versam, keine Haemophiliefälle aufgetreten sind, oder ob solche Fälle lediglich in die Kirchenbücher nicht aufgenommen wurden. Immerhin ist anzunehmen, daß, wenn in den letzten 200 Jahren in der Gemeinde Safien Bluter aufgetreten wären, diese von uns im Laufe unserer Nachforschungen höchstwahrscheinlich erfaßt worden wären (vgl. Allgemeiner Teil dieser Arbeit:

Erfassung der vor der Bestandesaufnahme 1952–1956 verstorbenen Bluter). Für die haemorrhagische Diathese des Propositus A IX. 10 gibt es somit folgende Erklärungsmöglichkeiten:

- a) Mutation zur Haemophilie.
- b) Auftreten einer nichthaemophilen Gerinnungsstörung.
- c) Eine von uns nicht erfaßte haemophile Vererbung, eventuell auf illegitimem Wege, die wir jedoch in Kenntnis der damaligen örtlichen Verhältnisse als unwahrscheinlich betrachten.

Es besteht kein Grund, den von HOESSLY-HAERLE, S. 348, angenommenen, hier bereits bei A VII. 7 erwähnten «atypischen Erbgang» anzunehmen.

HOESSLY-HAERLE, S. 344–348, bezeichnet A IX. 10 als «rudimentären Bluter», da sie außer seinen starken Nasenblutungen keine sonstigen Zeichen der Blutungsbereitschaft vom gleichen Gewährsmann wie wir (A IX. 11) übernommen hat. Unter konsequenter Beibehaltung der diagnostischen Kriterien, wie sie auch für alle meist spärlichen katamnestischen Angaben über die anderen Bluter von Tenna angewandt wurden, muß jedoch der *aus der Nase im Spital verblutete* A IX. 10 als Bluter angesehen werden.

Literaturangaben: HOESSLY-HAERLE, S. 344–348.

A IX. 14: Ursula H., von Safien, geb. 1888, † 1924 (Z. S.)
kopuliert 1913 mit A IX. 13 Johann Karl J., von Safien, geb. 1890,
† 1929 (Z. S.).

Entgegen der Annahme von HOESSLY-HAERLE, S. 344–346, kann die Proposita A IX. 14 nicht als «Teilbluterin» angesehen werden nur auf Grund der Tatsache, daß sie bei der sechsten Geburt verblutet ist, und weil ihre Eltern über männliche Vorfahren von A IV. 1 (siehe dort) abstammen.

Literaturangaben: HOESSLY-HAERLE, S. 344–346.

A X. 73: siehe B X. 531.

3. Nachfahrentafel Teil B

B III. 7: Samuel WALTHER, von Tenna, geb. 1676, † 1741 (K.T.)
kopuliert I° 1701 mit B III. 6 Marie JUON, von Safien,
† 1712 (K.T.)
kopuliert II° 1713 mit B III. 8 Anna GREDIG, von Safien,
† 1749 (K.T.).

Bluter: der erste im Kirchenbuch erwähnte Haemophiliefall, wörtlich: «hat 7 tag und nächst stets im mund geblüet, daran er gestorben ist als er erlebt hat 65 Jahr und 1 Monat».

Literaturangaben: HOESSLI. S. 16; HOESSLY-HAERLE, S. 306, 324–325, 350.

B VI. 51: siehe C VII. 191.

B VI. 95: Jöri JOOS, von Versam, geb. 1782, † 1790 (K.Ve.).

Bluter: nach GRANDIDIER. S. 59. Zeilen 3–4: «Anna Marie WEIBEL (B V. 60) heirathete den Jonas J. (B V. 59) in Arezen und hatte zwei Söhne (der Propositus: B VI. 95 und sein Bruder B VI. 96. siehe dort. Verf.), die sich beide in früher Jugend verbluteten.»

NB: B V. 59 hieß Jöri bzw. Georg J. und nicht Jonas J.; er hatte mit seiner Frau drei Söhne (B VI. 95, B VI. 96, B VI. 97).

Literaturangaben: GRANDIDIER. S. 59. Zeilen 3–4; HOESSLI, S. 17; HOESSLY-HAERLE, S. 353.

B VI. 96: Martin JOOS, von Versam, geb. 1789, † 1797 (K.Ve.).

Bluter: wie bei B VI. 95 (siehe oben).

B IV. 97: Jöri JOOS, von Versam, geb. 1791, † 1838 (K.Ve.)
kopuliert 1819 mit B VI. 98 Ursula GARTMANN, von
Safen, geb. 1788, † 1844 (K.Ve. und K.S.).

Bluter: nach HOESSLI. S. 17. «Georg, der auch Bluter war». er starb «an Rheumatismus» nach K.Ve.

Literaturangaben: HOESSLI, S. 17, HOESSLY-HAERLE, S. 353.

B VI. 99: Daniel GARTMANN, von Tenna, geb. 1781, † 1784 (K.T.).

Bluter: nach HOESSLI. im I. Stammbaum. Tab. IV, als Bluter aufgeführt. sonst keine näheren Angaben. vgl. HOESSLI. S. 17 «... die Descendenz (von B V. 61 und B V. 62) weist mehrere Bluter auf. doch bin ich leider nicht im Stande genauere Angaben zu machen».

Literaturangaben: HOESSLI. I. Stammbaum. Tab. IV, und S. 17; HOESSLY-HAERLE. S. 353 und Extratafel IV 4 zu Teil II des Stammbaumes.

B VI. 102: Daniel GARTMANN, von Tenna, geb. 1796, † 1802 (K.T.).

Bluter: nach GRANDIDIER. S. 58. Zeile 14. «Daniel G. verblutete sich im 6. Jahre».

NB: Bei HOESSLI im I. Stammbaum mit unrichtigem Todesjahr.

Literaturangaben: GRANDIDIER. S. 58. Zeile 14; HOESSLI. S. 17 und I. Stammbaum. Tab. IV; HOESSLY-HAERLE. S. 353 und Extratafel IV 4 zu Teil II des Stammbaumes.

B VI. 105: Daniel GARTMANN, von Tenna, geb. 1787, † 1809 (K.T.).
Bluter: nach GRANDIDIER, S. 58, Zeilen 8–9, «Daniel G., verblutete sich aus einer kleinen Wunde im 22. Jahre».

NB: Vater des B VI. 105 ist B V. 54 und heißt Michel GARTMANN und nicht wie bei HOESSLI, S. 17, Christian GARTMANN.

Literaturangaben: GRANDIDIER, S. 58, Zeilen 8–9; HOESSLI, S. 18;
 HOESSLY-HAERLE, S. 360.

B VI. 106: (auch C VII. 184): Martin GARTMANN, von Tenna, geb. 1789, † 1844 (K.T.)
 kopuliert 1816 mit B VI. 107 (auch C VII. 185) Elsbeth G., von Tenna, geb. 1797, † 1856 (K.T.).

Bluter: nach K.T. wörtlich: «Verblutung.»

Auch nach längerer Beschreibung von VIELI, S. 341–342, mit folgender Katamnese: zur Zeit der Beobachtung, im Dezember 1844, litt B VI. 106 das zweite Mal an Zahnfleischblutung, die bereits 4 Wochen trotz Extraktion des lockeren Zahnes und Tamponade andauerte. Der behandelnde Arzt, Dr. VIELI, versuchte verschiedene blutstillende Mittel, u.a. auch mechanische Tamponade mit teilweise gutem Resultat. Sechzehn Tage nach der Behandlung starb der Patient, ohne daß der Arzt gerufen oder genauer informiert wurde; als Todesursache nimmt VIELI die Verblutung an.

NB: Unrichtiges Sterbealter bei VIELI, S. 343, und bei GRANDIDIER, S. 61. Bei GRANDIDIER, S. 61, der Name des B VI. 106 irrtümlicherweise zu GÄRTNER verändert.

Literaturangaben: VIELI, S. 341–342; GRANDIDIER, S. 58, Zeilen 10–11, und S. 61–62; HOESSLI, S. 18; HOESSLY-HAERLE, S. 306, 320, 360.

B VII. 104: siehe C VII. 201.

B VII. 168: Philipp Z., von Süs und Ilanz, geb. 1805, † 1836 (K. Ilanz und K. Chur)

kopuliert I° 1834 mit B VII. 167 Augusta CANDRIAN,
 von Duvin, geb. ?,
 † ? (K. Pitasch)

kopuliert II° 1836 mit B VII. 169 Margaret NUTTLI, von
 Ilanz, geb. 1810,
 † 1877 (K. Ilanz)

Bluter: nach GRANDIDIER, S. 58, Zeile 17, «... ein Sohn (von B VI. 100 und B VI. 101) hat sich todt geblutet, der andere lebt noch». Bei dem Verbluteten mußte es sich um den Propositus B VII. 168 handeln, da die

Bestandesaufnahme von VIELI für GRANDIDIER schon nach dem Tode des Propositus B VII. 168 erfolgte, so daß der damals noch lebende Bruder nur Domenicus B VII. 166, geb. 1812, † ? (K. Sagens) sein konnte.

Literaturangaben: GRANDIDIER, S. 58, Zeile 17; HOESSLY-HAERLE, S. 354.

B VII. 175: (auch A VII. 44): Philipp JEHLI, von Versam, geb. 1811, † 1862 (Z.Ve.)

kopuliert 1836 mit B VII. 176 (auch A VII. 45) Anna B., von Safen, geb. 1814, † 1862 (Z.Ve.).

Bluter: nach K.Ve. wörtlich als Todesursache: «An den Folgen eines Falls auf den Futtertrog. Er gehörte zu den Blutern.»

Auch nach längerer Beschreibung bei GRANDIDIER, S. 62–64, angegeben vom behandelnden Arzt Dr. VIELI, mit folgender Katamnese: erste Symptome der Blutungsbereitschaft im 10. Lebensjahr, erster bedeutender Anfall im 23. Lebensjahr (ohne nähere Angaben). von dieser Zeit an bis zum Moment der Beobachtung im Februar 1854 litt der Patient 1 bis 2 Mal im Jahr an Blutungserscheinungen. «Gewöhnlich zeigt sich der Anfall als bedeutende Anschwellung des rechten Schenkels von der Hüfte abwärts bis zum Fußgelenk; läßt er nach, so wird das ganze Bein schwarz. ... auch trinkt er dann nur kaltes Getränk, zuweilen in einer Nacht 16 Maaß kalten Wassers (1 Maaß = $1\frac{1}{2}$ Liter, Verf.). Von starken Blutungen blieb er bisher verschont; hat der Anfall den höchsten Grad erreicht, so tritt Kopfschmerz bis zur Ohnmacht ein, dann zeigten sich einige Tropfen Blut aus der Nase, und damit ist die Krise eingetreten und tritt schnelle Besserung ein. ... Die Anfälle sollen gewöhnlich gegen 3 Wochen dauern und gern in der kälteren Jahreszeit eintreten.»

Literaturangaben: GRANDIDIER, S. 62–64; HOESSLY-HAERLE, S. 306, 322, 350, 355.

B VII. 178: Maria Barbara JEHLI, von Versam, geb. 1813, † 1843 (Z.Ve.)

kopuliert 1835 mit B VII. 177 Christian J., von Versam, geb. 1801, † 1859 (K.Ve. und Z.Ve.).

Entgegen der Annahme von HOESSLY-HAERLE, S. 322, 349, 358, kann B VII. 178 nicht als «Teilbluterin» angesehen werden, nur auf Grund der Tatsache, daß sie bei der dritten Geburt verblutet ist.

Literaturangaben: GRANDIDIER, S. 58–59; HOESSLY-HAERLE, S. 322, 349, 358.

B VII. 180: Benedikt JEHLI, von Versam, geb. 1824, † 1831 (K.Ve. und Z.Ve.).

Bluter: nach K.Ve. wörtlich: «Verblutet.»

Bei GRANDIDIER, S. 58, Zeilen 21–24: «Anna G. verheiratete sich an J. in Arezen, hatte 2 Söhne und 3 Töchter (in Wirklichkeit 2 Söhne und 4 Töchter, Verf.); der älteste Sohn starb an Blutung in Folge eines Steinwurfs; der zweite hatte bisher 6 gesunde Töchter....»

Es liegt hier wohl die Verwechslung der beiden Söhne vor, indem der jüngere (Propositus B VII. 180) mit 7 Jahren nach K.Ve. (siehe oben) an Verblutung starb, der ältere (B VII. 175) aber 8 Töchter hatte. Somit kann angenommen werden, daß der von GRANDIDIER wie oben beschriebene Bluter mit dem Propositus B VII. 180 identisch ist.

NB: Die Angaben aus den Kirchenbüchern betreffen K.Ve. und nicht Kirchenbuch Arezen, wie HOESSLY-HAERLE, S. 355, angibt; Arezen ist nur ein Weiler von Versam, und es existiert kein Kirchenbuch von Arezen.

Literaturangaben: GRANDIDIER, S. 58, Zeilen 21–24, HOESSLY-HAERLE, S. 355.

B VII. 183: Margret JEHLI, von Versam, geb. 1825, † 1905 (Z. Schnaus)
kopuliert 1845 als zweite Frau mit B VII. 182 Johann Peter C., von Schnaus,
geb. 1810, † 1897 (Z. Schnaus).

Entgegen der Annahme von HOESSLY-HAERLE, S. 322–349, 359, kann B VII. 183 nicht als «Teilbluterin» angesehen werden, nur auf Grund der Tatsache, daß von ihren *vierzehn* Schwangerschaften vier abortiv mit starken Blutungen verliefen.

Nach GRANDIDIER, S. 58, Zeilen 27–31: «... (B VII. 183) hatte zuerst einen Sohn, der sich in früher Jugend verblutete, später abortierte sie viermal unter starker Blutung. Bei der nächsten Schwangerschaft verordnete man eine knappe, reizlose Diät und kleine Gaben Mutterkorn, worauf sie einen gesunden ... Knaben gebar.»

HOESSLY-HAERLE übernimmt die Angaben vollständig aus GRANDIDIER, spricht aber S. 322, 349, 359 von «außerordentlich» starken Abortblutungen.

Literaturangaben: GRANDIDIER, S. 58, Zeilen 27–31; HOESSLY-HAERLE, S. 322, 349, 359.

B VIII. 216: Lorenz E., von Versam, geb. 1828, † 1896 (K. und Z.Ve.)
kopuliert 1851 mit B VIII. 217 Margret MANI, von Andeer,
geb. 1827, † 1915 (K. und Z.Ve.).

Bluter: nach GRANDIDIER, S. 59, Zeilen 7–8: «Anna Maria (B VII. 153), verheirathete U. (fälschlicherweise an Stelle von E., Verf.), hatte einen Sohn (B VIII. 216), der zwar Bluter ist, aber gesunde Kinder hat,»

Literaturangaben: GRANDIDIER, S. 59, Zeilen 7–8; HOESSLY-HAERLE, S. 353.

B VIII. 224: Johann Martin B., von Versam, geb. 1838, † 1896 (Z.Ve.)
kopuliert 1863 mit B VIII. 225 Ursula BUCHLI, von Versam, geb. 1846,
† 1912 (Z.Ve.).

Entgegen der Annahme von HOESSLY-HAERLE, S. 348, 353, kann B VIII. 224 nicht als «rudimentärer Bluter» bezeichnet werden, und zwar aus folgenden Gründen:

- 1) Nach GRANDIDIER, S. 59, Zeile 11; «Barbara (B VII. 155), verheiratete B., hat bis jetzt 2 gesunde Söhne», d.h. B VIII. 223, geb. 1830, (Z.Ve.) und den Propositus B VIII. 224, der zur Zeit der Berichte von VIELI an GRANDIDIER etwa elf Jahre alt war. Es kann sich dabei nur um die hier angegebenen zwei Brüder handeln, da der Erstgeborene B VIII. 222, geb. 1829, (Z.Ve.) im ersten Lebensjahr gestorben ist.
- 2) HOESSLI erwähnt den Propositus nur im Stammbaum, und zwar als gesund; zur Zeit der Untersuchung von HOESSLI war aber der Propositus bereits 40 Jahre alt.
- 3) HOESSLY-HAERLE, S. 353, schreibt: «Von den drei Söhnen (B VIII. 222, B VII. 223, B VIII. 224) der zweiten Tochter (B VII. 155) waren zwei ganz gesund, der dritte J.M.B.v.V. zeigte als einziges Symptom seiner hämophilen Abstammung auffallend lange Blutungen nach Verletzungen, wie mir sein noch lebender Schwager mitteilte. Da er sonst keinerlei Zeichen von Haemophilie hatte, zählte ich ihn unter die Rubrik der sogenannten ‚rudimentären Bluter‘, bei denen gewissermaßen nur noch spärliche Reste des Erbübels in Erscheinung treten.»

Somit ist in den zeitgenössischen Berichten von GRANDIDIER und HOESSLI nichts über etwaige Blutungsbereitschaft des Propositus B VIII. 224 zu finden. Auch unsere Nachforschungen bei seiner Familie und Nachkommen gaben uns keinen Grund, bei ihm Blutungstendenz anzunehmen.

Literaturangaben: GRANDIDIER, S. 59, Zeile 11; HOESSLI, I. Stammbaum, Tab. IV.; HOESSLY-HAERLE, S. 348, 353.

B VIII. 248: siehe C VIII. 328.

B VIII. 256: (auch C IX. 390) Ursula JEHLI, von Versam, geb. 1853, † 1892 (Z. Val) kopuliert 1882 als erte Frau mit B VIII. 257 (auch C IX. 391) Peter G., von Valendas, geb. 1855, † 1930 (Z. Val).

PIANTA, S. 195, rechnet sie unter «Konduktorinnen mit Blutungsbereitschaft» und schreibt über sie: «Auch sie hatte bei den Geburten erhöhte Blutungsneigungen. Starke Blutungen traten bei ihr auch bei Zahnextraktionen auf. Man hat ihr oft Blut entnommen. Nach einer Blutegelwunde konnte nur mit Mühe das Blut gestillt werden. Während des Klimakteriums sind bei ihr starke uterine Blutungen aufgetreten.»

Die Proposita ist 60 Jahre vor der Bestandesaufnahme von PIANTA verstorben. Sie lebte zur Zeit der Untersuchungen von HOESSLI und stammt aus einer Bluterfamilie, so daß anzunehmen ist, daß HOESSLI auf ihre vermeintliche Blutungsbereitschaft aufmerksam geworden wäre; wir wissen jedoch, daß er Blutungserscheinungen bei Frauen durchwegs bestreitet. Auch HOESSLY-HAERLE, welche eine Generation vor PIANTA die Bestandesaufnahme durchführte und nach «Bluterinnen» Ausschau hielt, weiß nichts über Blutungserscheinungen bei der Proposita zu berichten.

Genitalblutungen als Beweis von Blutungsbereitschaft der Frauen haben wir bereits im allgemeinen Teil dieser Arbeit ablehnen müssen; die Proposita hat übrigens 6 Kinder zur Welt gebracht, was wohl nicht für ihre Blutungsbereitschaft spricht. Bei den bekannten Nachblutungserscheinungen der Blutegelwunden ist anzunehmen, daß sich eine an Blutungsneigung leidende Frau solche nicht hätte setzen lassen. Im Laufe unserer Nachforschungen haben wir nichts über angebliche Blutungstendenz der Proposita in Erfahrung bringen können. Nach den von uns angenommenen Richtlinien kann sie nicht als Konduktorin mit Blutungserscheinungen angesehen werden.

Literaturangaben: HOESSLY-HAERLE, S. 357; PIANTA, S. 167; FONIO, S. 24, 81.

B VIII. 265: Christian (de?) C., von Schnaus, geb. 1842, ausgewandert nach Amerika, † ? (K.Ve. und Z. Schnaus)
kopuliert 1871 mit B VIII. 266 Catharina BRUNETT, von Urmein, geb. 1846, † 1873 (Z. Schnaus).

Bluter: nach GRANDIDIER, S. 58, Zeilen 24–25: «Von den 3 Töchtern verheirathete sich eine (B VII. 181) und starb früh im Wochenbette, ihr Sohn (B VIII. 265) ist Bluter.»

Das Auswanderungsdatum des Propositus B VIII. 265 nach Amerika kann nicht ermittelt werden, jedoch ist sein zweiter Sohn (B IX. 350) im Jahre 1873 noch vor der Auswanderung geboren (Z. Schnaus), so daß wir den Propositus bis zu seinem 31. Lebensjahr verfolgen können.

Während der Drucklegung haben wir auf unsere Anfrage hin von Dr. Charles M. WOOLF, Laboratory of Human Genetics, Division of Biology, University of Utah, Salt Lake City, USA, einen Brief, datiert vom 14. Januar 1958, erhalten, worin einige Angaben über den Propositus enthalten sind. Zur Vervollständigung der vorliegenden Arbeit geben wir den Brief auszugsweise wieder:

«Information is available for Christian Carisch (Carrish) but it is not very informative for a genetic study of hemophilia. According to the records on file here he was born 24 January 1842 in Schmaus, Graubünden, Switzerland. He was married three times. The first wife was Cathrine (Katharina) Brunett. She was born 4 January 1846 in Urmein, Switzerland. She died 12 December 1873. The second wife was Johanna Christine Worbs who was born 29 July 1825 in Grendsdorf, Schlesien, Switzerland. Date of death not given. The third wife was Marianna Filsiana who was born in Filehene, Poland. Date of birth and death not given.

According to all available information on file in the index bureau of the genealogical offices, Christian Carisch only had offspring by the first wife Cathrine Brunett. The other wives seemed to have come along when he was about 50 years old but the records are not clear on this point. The records are also not clear as to whether the last two wives were polygamous or came along one by one. The latter situation was probably the case since at that time the Church prohibited polygamous marriages, i.e., since about 1890.

The son (Johann Peter Carisch) of Christian and Cathrine who lived past childhood was born 17 May 1872 in Graubünden, Switzerland, and died (according to the records here) on November 13, 1890. I notice that your records show a different date of death for this individual. He married Ursula John but there is no record of any children resulting from this mar-

riage. If he died at age 18 there wasn't much time for children to result from this marriage since he could not have been married too long.

There is no definite date given for the death of Christian Carisch. He was alive in 1893 and residing in Salt Lake City, Utah. Death certificates for the state of Utah do not begin until 1905. There is a death certificate in the Utah State Vital Statistics Departement for a Christian Carrish, born January 26, 1835 in Switzerland (parents unknown), who died August 7, 1918 in Salt Lake City, Utah. The cause of death was listed as arteriosclerosis. This may or may not be the gentleman in question. There is a discrepency in date of birth but death certificates at that time were often not accurate. It is very likely that this is the Mr. Carisch you are interested in. If so, hemophilia did not appear to shorten his life any. Or was he not affected? The local hospitals have destroyed their records for this period of time so nothing can be determined of his medical history from that source. sig. Charles M. Woolf»

Literaturangaben: GRANDIDIER, S. 58, Zeilen 24–25; HOESSLY-HAERLE, S. 358.

B VIII. 268: Pankraz C., von Schnaus, geb. 1846, † 1851 (Z. Schnaus).

Bluter: nach GRANDIDIER, S. 58, Zeilen 26–28: «... die zweite Tochter (BVII.183) heirathete den Mann (BVII.182) ihrer verstorbenen Schwester, hatte zuerst einen Sohn (B VIII. 268), der sich in früher Jugend verblutete....» Nach HOESSLY-HAERLE, S. 359, ist die Blutungstendenz des Propositus durch seine Schwester B VIII. 278, geb. 1864, † 1933 (Z. Schnaus) bestätigt worden, die über eine sehr lange Blutung des Propositus nach einer Schnittverletzung am Finger zu berichten wußte.

Literaturangaben: GRANDIDIER, S. 58, Zeilen 26–28; HOESSLY-HAERLE, S. 359.

B IX. 242: Johannes B., von Valendas, geb. 1882, † 1909 (Z. Val.).

Bluter: nach HOESSLY-HAERLE, S. 351–352: «Nach ärztlicher Aussage war er (B IX. 242) ein typischer Bluter; Eine Pfeilverletzung am Munde, im Schulalter durch einen Knaben beigebracht, erzeugte eine unstillbare Blutung der Lippe, die in typischer Weise erst am zweiten Tag nach der Verletzung auftrat. Auch sonst hatte der Knabe typische Bluterzeichen, wie Hämatome und Gelenkergüsse nach geringfügigen Insulten, nach dem Zeugnis eben dieses Schulkameraden.»

Todesursache: Appendicitis (K.Val.).

Literaturangaben: HOESSLY-HAERLE, S. 351–352.

B IX. 308: Johann Nicolaus Z., von Ilanz, geb. 1878, † 1920 (Z. Ilanz)
 kopuliert 1911 mit B IX. 309 Ursula W., von Maienfeld, geb. 1884, † 1956
 (Z. Ilanz).

HOESSLY-HAERLE, S. 354, schreibt: «... der bei den *rudimentären Blutern* erwähnte Johann Nicolaus Z. (B IX. 308) von I., litt nach persönlicher Aussage seiner Frau und des behandelnden Spitalarztes, an multiplen, fast unstillbaren Lungenblutungen, die mit Koagulen bekämpft wurden (im letzten Lebensjahre hatte er zehn Lungenblutungen und starb zwei Tage nach der letzten Blutung). Auch Zahnfleischblutungen und Druckbeulen traten hie und da auf.»

Der von uns befragte Sohn B X. 438, Hans Joachim Z., geb. 1913, in Ilanz, kann sich an seinen Vater B IX. 308 gut erinnern, trotzdem er bei seinem Tode erst 7 Jahre alt gewesen ist, und weiß auch gut Auskunft aus den Berichten seiner 1956 verstorbenen Mutter B IX. 309. Der Vater war Zimmermann, ein Beruf, bei dem Verletzungen häufig sind, doch hat der Sohn nie etwas von einer erhöhten Blutungsbereitschaft des Vaters vernommen. Er weiß auch nichts über seine angeblichen Zahnfleischblutungen und Druckbeulen zu berichten, wohl aber über seine langjährige *Lungentuberkulose* und kann sich noch an die letzte Lungenblutung erinnern. Nach unseren weiteren Erkundigungen kommen in der Familie des Propositus mehrere Fälle von Tuberkulose vor, an der auch der Propositus selbst gestorben ist; damit wären auch seine Lungenblutungen zu erklären. Bei der umstrittenen Wirksamkeit der angewandten Coagulentherapie würde ein haemophiler Patient keine zehn Lungenblutungen in einem Jahre erleben können.

HOESSLY-HAERLE erwähnt die Tuberkulose des Propositus überhaupt nicht, trotzdem diese eine naheliegende Erklärung seiner Lungenblutungen darstellt.

Nach den von uns angenommenen Richtlinien kann der Propositus B IX. 308 nicht als «rudimentärer Bluter» bezeichnet werden.

Literaturangaben: HOESSLY-HAERLE, S. 347–348, 354.

B IX. 320: Johanna W., von Valendas, geb. 1879, † 1927 (Z. Kästris)
 kopuliert 1901 mit B IX. 319 Benedikt S., von Kästris, geb. 1879, lebt
 in Ilanz (Z. Kästris).

PIANTA, S. 176, 195, schreibt der Proposita Blutungsneigung zu, mit folgender Begründung, S. 176: «Der Pat. (B X. 464, Verf.) will nichts von Blutungen bei ihr wissen. Dr. CAHANES-CATHOMAS (wohl Dr. J. B. Cathomas, damaliger Spitalarzt in Ilanz, Verf.) jedoch berichtet mir, daß sie an einer Ulkusblutung gestorben sei.»

Eine Ulkusblutung ohne jegliche andere Zeichen der Blutungsbereitschaft kann als Beweis der Blutungsneigung diskussionslos abgelehnt werden. Im übrigen starb die Proposita an ihrer Ulkusblutung zur Zeit der Bestandesaufnahme von HOESSLY-HAERLE, die jedoch nichts über eine Blutungsneigung bei ihr zu berichten weiß. Unsere Nachforschungen geben ebenfalls keinen Grund zur Annahme einer Blutungsbereitschaft bei der Proposita.

Literaturangaben: HOESSLY-HAERLE, S. 356; PIANTA, S. 176, 195.

B IX. 323: Edwin H., von Wolfhalden, App., geb. 1881, ausgewandert
 1911 nach Amerika, lebt in Greenwood, Wisconsin (Z. Wolfhalden und pers. Mitteilung der Schwester B IX. 322 des Probanden, vom Dezember 1955), kopuliert 1908 mit B IX.
 324 Katharina S., von Heiden, App., geb. 1887, lebt in
 Greenwood, Wisc. (Quellenangaben wie oben).

Bluter: nach HOESSLY-HAERLE, S. 357: «... (B IX. 323), der schon seit Jahren in Amerika lebt und auch heute noch stark unter Blutungen und Haematomen zu leiden hat. ... verblutete..., vor Jahren beinahe an einer Zahnextraktion in der Rekrutenschule Basel. Auch als Kind war er öfters in Lebensgefahr durch Blutungen.»

Nach den uns von B IX. 322. Schwester des Probanden, mitgeteilten Angaben, bekommt der zurzeit 75jährige Proband gelegentlich Haematome und Suffusionen, er arbeitet noch in seinem Wagnerberuf. B IX. 322 weiß von anderen Zeichen der Blutungsbereitschaft ihres Bruders nichts zu berichten; sie hat ihn im Sommer 1955 besucht.

Literaturangaben: HOESSLY-HAERLE, S. 357.

B IX. 331: Barbara G., von Valendas, geb. 1885, † 1935 (P. Z. S.)
kopuliert 1909 als erste Frau mit B IX. 330 Johann Martin G., von Safien,
geb. 1881, † 1947 (Z. S.).

Nach HOESSLY-HAERLE, S. 349, unter «Frauen mit Teilblutungen», Zeile 23: «... (B IX. 331) hatte nach ihrer persönlichen Aussage sehr starke Blutungen bei Geburten.»

PIANTA, S. 167, Zeilen 15–18, Katamnese 12 Jahre nach dem Tode der Proposita aufgenommen: «Es sind bei ihr starke extramensuelle, uterine Blutungen vorgekommen. Ebenso sollen bei den Geburten jedesmal abnorm starke Blutungen aufgetreten sein.»

Die Proposita und ihre Familie gehörten zu unseren Patienten bzw. deren engstem Verwandtenkreis. Alle ihre Kinder (vgl. die Nachfahrentafel Teil B) wurden von uns für die vorliegende Arbeit untersucht. Es ist uns bekannt, daß die Proposita von stärkeren Blutungen bei Geburten gesprochen hat; es handelte sich wohl damals bei ihren 8 Geburten im Laufe von 11 Jahren um atonische Uterusblutungen. Bei einer auch partiellen Blutungstendenz hätte sie wohl die 8 rasch aufeinanderfolgenden Geburten nicht ohne weiteres überstanden. Sie gehört zu einer Bluterfamilie, wo eine Blutungstendenz bald bemerkt wird, doch ist ihren Verwandten nichts über ihre angebliche Blutungsbereitschaft bekannt.

Nach den angenommenen Richtlinien kann die Proposita von uns nicht als eine «Frau mit Teilblutungen» bezeichnet werden.

Literaturangaben: HOESSLY-HAERLE, S. 349, Zeile 23, S. 358, Zeilen 13–15; PIANTA, S. 167, Zeilen 15–18; FONIO, S. 24, S. 81, Zeilen 25–26.

B X. 444: Elsbeth R., von Kästris, geb. 1894, lebt in Valendas
(P.Z. Kästris).

Mögliche Konduktorin, wie aus Tafel 5 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 17. Juli 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B X. 450: Verena R., von Kästris, geb. 1902, lebt in Valendas
(P.Z. Kästris).

Nach HOESSLY-HAERLE, S. 349, Zeilen 27–30, unter «Frauen mit Teilblutungen» aufge-

führt, auch S. 355–356: «Bei den 11 Kindern dieser Ehe (B IX. 317 und B IX. 318) zeigten sich bis 1929 keinerlei Zeichen von Haemophilie. Da bekam die 27 jährige Tochter V. R. (B X. 450) nach einer Zahnextraktion, im Laufe des darauffolgenden Tages, eine profuse Zahnfleischblutung, so daß sie in der Nacht ‚beckenweise‘ Blut verlor und der Spitalarzt benachrichtigt werden mußte. Dieser fand das Mädchen in stark ausgeblutetem Zustande und schließlich gelang es ihm, mit Koagulen die Blutung zum Stillstand zu bringen. (Nach dem Berichte des Dr. C. zeigte das Blut ‚herabgesetzte Gerinnungsfähigkeit‘). Es handelt sich also hier um eine ‚Teilblutung‘ bei einer Frau aus einer Bluterfamilie.»

Die Probandin ist uns seit 1934 als Patientin bekannt. Über die Blutung nach Zahnextraktion berichten die Probandin und ihre älteste Schwester B X. 444 übereinstimmend, daß die Blutung in der Nacht nach der Extraktion aufgetreten sei und bis gegen Mittag angehalten habe.

Abgesehen von dieser Blutung hat die Probandin bis Ende 1955 keine Blutungsbereitschaft aufgewiesen: Menses ohne besondere Blutung, Schnittwunden bluten kaum, 1932 Kropfoperation ohne besondere Blutung, 1935 Extraktion von 6 Zähnen des Unterkiefers ohne besondere Blutung und ohne Nachblutung.

Somit kann die Probandin nach den von uns angenommenen Richtlinien nicht als «Frau mit Teilblutungen» bezeichnet werden.

Die Proposita ist mögliche Konduktorin, wie aus Tafel 5 ersichtlich. Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 17. Juli 1956: normale Gerinnungswerte.

Literaturangaben: HOESSLY-HAERLE, S. 349, Zeilen 27–30, S. 355–356.

B X. 456: Julia R., von Kästris, geb. 1909, lebt in Riein (P.Z. Kästris).
kopuliert 1932 mit B X. 455 Jochen C., von Riein, geb. 1907,
lebt in Riein (Z. Kästris).

Mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 17. November 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B X. 460: Barbara R., von Kästris, geb. 1914, lebt in Ilanz (P.Z. Kästris)
kopuliert 1914 mit B X. 459 Johann Jakob H., von Ilanz,
geb. 1913, lebt in Ilanz (Z. Kästris).

Sichere Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 17. November 1956: normale Gerinnungswerte.

Literaturangaben: Nicht beschrieben.

B X. 464: Georg S., von Kästris, geb. 1904, lebt in Ilanz (P.Z. Kästris),
kopuliert 1930 mit B X. 465 Sidonia O., von Strada, geb.
1904, lebt in Ilanz (P. Z. Kästris).

Bluter: Nach HOESSLY-HAERLE, S. 307, 356 und PIANTA, S. 175–176, nach persönlichen Mitteilungen des behandelnden Arztes Dr. J. BUNDI, Ilanz, nach gerinnungsphysiologischer Untersuchung von Dr. M. GEIGER (Gerinnungsphysiologisches Labor, Kantonsspital Zürich) und nach der von uns aufgenommenen Anamnese:

Anamnese (nach unserem Fragebogen, vgl. S. 32–33, zusammengestellt):

Die Blutungsbereitschaft erstmals im 4.–5. Lebensjahr des Probanden, anlässlich einer kleinen Schnittverletzung beobachtet.

In der *Jugend* sehr starke Blutungen nach geringfügigen Verletzungen. Typische haemophile Nachblutung (im Sinne von SCHLOESSMANN, S. 32 ff.): zuerst scheinbares Aufhören der Blutung, die Wunde deckt sich mit einer Fibrinschicht, durch welche dann in 1 bis 3 Tagen eine sickernde Nachblutung einsetzt. Diese dauerte manchmal 6 bis 8 Wochen. Vor der endgültigen Heilung blieben die Verletzungen wochenlang mit einer Fibrinkruste bedeckt; ihr Aufreißen führte zu erneuten langdauernden Blutungen. *Im Erwachsenenalter hat bei dem Probanden die Blutungsbereitschaft nach Verletzungen stark abgenommen*, was bereits von HOESSLY-HAERLE, 1930, S. 307, bei dem damals 25jährigen Probanden beobachtet wurde. Der Proband konnte und kann ohne weiteres seinem Beruf als Bauinstallateur der sanitären Anlagen nachgehen, trotzdem dieser mit erhöhten Verletzungsgefahren verbunden ist. Er sagt aus, daß *seine Verletzungen und Schürfungen seit mehreren Jahren normal abheilen*, meint jedoch, daß *seine übrige Blutungstendenz mit dem Alter nicht abgenommen hat*, sondern lediglich infolge größerer Schonung weniger in Erscheinung tritt.

Suffusionen sind sehr stark im Kindesalter aufgetreten, kommen jetzt nur selten vor, was der Proband auf größere Schonung seinerseits zurückführt.

Blutungen in die Weichteile sind mehrmals aufgetreten und haben wochenlange Arbeitsunfähigkeit verursacht.

Öftere Blutungen aus der Gingiva, so daß der Proband die Zähne nicht putzen kann. Einer Zahnextraktion im 12. Lebensjahr folgte eine 14tägige Nachblutung, die fast zum Verblutungstod führte (bestätigt durch die Aussage des Spitalarztes Dr. CATHOMAS bei HOESSLY-HAERLE, S. 356).

Epistaxis kommt oft vor, besonders bei Erkältungen, in Form von sickernder Blutung, die bis 3 Wochen andauern kann.

Gelenkblutungen sind öfters vorgekommen. Im re. Fußgelenk Haemarthros seit Adoleszenz; die Bewegung im Gelenk ist stark eingeschränkt, Schmerzen bei stärkerer Beanspruchung. Letzte Exacerbation 1949 mit Schwellung des Gelenkes (Dr. BUNDI).

Röntgenologischer Befund einer Aufnahme aus dem Spital St. Nikolaus, Ilanz, vom 30. November 1956 (vgl. Fig. 5), begutachtet von Dr. W. PREIBISCH, Röntgeninstitut der Universität Bern:

Beide Fußgelenke antero-posterior und seitlich: Im Bereiche des oberen Sprunggelenkes beiderseits ist der Gelenkspalt etwas verschmälert, jedoch unregelmäßig begrenzt, mit deutlichen Randwulstbildungen, die sich zackenförmig, insbesondere an den äußeren Gelenkrändern, darstellen. An den Gelenkflächen erkennt man deutliche Randusuren. Die benachbarten Skelettanteile zeigen unregelmäßige Verdichtungen: Verdacht von cystischen Aufhellungen. Zeichen für frische entzündliche Veränderungen sind nicht nachweisbar.

Der Gelenkspalt des unteren Sprunggelenkes ist nicht verschmälert und bis auf den dorsalen Anteil glatt begrenzt.

Diagnose: hochgradige arthrotische Veränderungen im Bereiche der beiden oberen Sprunggelenke.

Seit mehreren Jahren haemarthrotische Beschwerden im re. Kniegelenk nach früheren Blutungen in die Gelenkkapsel.

1947 Schwellung des li. Handgelenkes (Dr. BUNDI).

1955 Blutung in die Cauda equina (Dr. BUNDI), Symptome: Schmerzen beim Sitzen, gelegentlich beim Wasserlösen, *Lasègue* positiv.

1948 Ösophagusblutung (bestätigt von PIANTA, S. 176): Blutgeschmack im Mund, mehrmals täglich hinauswürgen von Gerinnseln. Die Blutung hörte nach 10 Tagen unbehandelt auf. Sonstige viscerale Blutungen wurden nicht beobachtet.

Der Proband erklärt, bei Indispositionen unter verstärkter Blutungstendenz zu leiden.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 29. September 1956: Haemophilie B.

Literaturangaben: HOESSLY-HAERLE, S. 307, 356; PIANTA, S. 175–176; FONIO, S. 82, Zeilen 15–23.

B X. 467: Anna Margreth S., von Kästris, geb. 1910, lebt in Lenzburg (E. Lenzburg), kopuliert 1940 mit B X. 466 Alois K., von Sarmenstorf AG, geb. 1910, lebt in Lenzburg (E. Lenzburg).

Sichere Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48 am 15. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B X. 478: Johann Martin G., von Safien, geb. 1910. lebt in Chur (E. Chur und Z. S.)
 kopuliert 1936 mit B X. 479 Marie N., von Felsberg, geb. 1910, lebt in Chur (E. Chur).

Bluter: Nach HOESSLY-HAERLE, S. 357, PIANTA, S. 165–167, nach Krankengeschichte des Kantonsspitals Chur, gerinnungsphysiologischer Untersuchung Dr. M. GEIGER (Gerinnungsphysiologisches Labor, Kantonsspital Zürich) und nach der von uns aufgenommenen Anamnese.

Anamnese (nach unserem Fragebogen, vgl. S. 32–33, zusammengestellt):

Die Blutungsbereitschaft des Probanden hat sich erstmals mit 12 bis 14 Jahren manifestiert, und zwar durch eine sehr starke Nachblutung aus einer Schnittverletzung am Finger, mit mehrstündigem blutungsfreiem Intervall unmittelbar nach der Verletzung (bestätigt durch HOESSLY-HAERLE, S. 357). Seitdem kamen bei dem Probanden stets mehrtägige Blutungen nach Verletzungen vor.

Suffusionen traten auf, wenn auch selten, da der Proband in seinem Beruf als Beamter und auch außerberuflich keinen schweren physischen Arbeiten nachgeht; nach dem Schießen traten Suffusionen an der Schulter auf (bestätigt durch PIANTA, S. 167).

Muskelhaematome traten nach Kontusionen auf. Mit 16 Jahren trat ein großes Haematom in der Hüftmuskulatur als Folge eines Hufschlages in diese Gegend auf (bestätigt durch HOESSLY-HAERLE, S. 357). 1946, laut Krankengeschichte des Kantonsspitals Chur, schweres Kontusionshaematom im Bereiche der Hüft-, Ober- und Unterschenkelmuskulatur nach einem Sturz aufs Knie beim Skifahren.

Kleine Blutungen aus der Gingiva traten beim Zähneputzen auf. Einer Backenzahnextraktion oben links im 16. 17. Lebensjahr folgte eine 2 bis 3 Tage dauernde starke Blutung, die nach Aussagen des Probanden einen starken Haemoglobinabfall verursachte.

Oft Epistaxis, mehrere Tage nacheinander in Schüben auftretend. 1946 infolge einer anhaltenden Nasenblutung im Kantonsspital Chur hospitalisiert. Nach dortiger Krankengeschichte konnte die Blutung 4 Tage lang nicht gestillt werden, trotz vorderer und hinterer Tamponade. Es wurde auch Coagulen erfolglos versucht. Die Blutung stand erst auf eine Bluttransfusion, wobei in den 4 Tagen der Blutungsdauer das Haemoglobin von 94% auf 54% gesunken war. Anlässlich des Spitaleintrittes wurde gemessen:

Blutungszeit 1' 55''

Gerinnungszeit (BÜRGER): Fadenbildung 3' 15'', total 4' 40''

Prothrombinzeit (QUICK): 43''



Fig. 5 Röntgenaufnahme der Sprunggelenke von B X. 464, vom 30. November 1956
Ankle joints of B X. 464, radiograph of 30th November 1956

Nach Aussage des Probanden hat bei ihm das Nasenbluten schon oft zu Haemoglobinwerten von 40%, einmal sogar zu 23%, geführt.

Kniegelenkhaematom 1946, anlässlich des beschriebenen Sturzes beim Skifahren. Sonst keine haemarthrotischen Veränderungen und Beschwerden.

1945 Behandlung im Kantonsspital Chur wegen Ösophagusblutung mit Haematemesis. Harnblutungen traten von Zeit zu Zeit auf, worauf der Proband einige Tage liegen blieb.

Blutungen in das Zentralnervensystem sind nicht vorgekommen.

Die Abnahme der Blutungsbereitschaft mit dem Alter wurde von der Mutter des Probanden bereits HOESSLY-HAERLE (1930). S. 307. mitgeteilt. Auch nach Aussage des Probanden *sind die Blutungserscheinungen im Laufe der Jahre stark zurückgegangen, seit 1946 habe er keine Blutungen mehr gehabt.*

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 28. September 1956: Haemophilie B.

Literaturangaben: HOESSLY-HAERLE. S. 307, 357; PIANTA. S. 165–167; FONIO, S. 81, Zeilen 19–28.

B X. 481: Ursula G., von Safien, geb. 1911, lebt in Chur (E. Chur)
kopuliert 1938 mit B X. 480 Luzius J., von Praden, geb. 1912,
lebt in Chur (E. Chur).

Mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 21. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B X. 482: Peter G., von Safien, geb. 1912, lebt in Malans. (Z. Safien)
kopuliert 1939 mit B X. 483 Maria Anna P., von Udes (Bez.
Schwaz), Deutschland, geb. 1915, lebt in Malans (Z. Safien).

Bluter: nach HOESSLY-HAERLE. S. 357–358. PIANTA. S. 167–169, nach Krankengeschichten des Kantonsspitals Chur, Akten der Eidgenössischen Militärversicherung (insgesamt 114 Aktenstücke), Akten der Schweiz. Unfallversicherungsanstalt, nach persönlichen Mitteilungen des behandelnden Arztes Dr. H. MARX, Malans, nach gerinnungsphysiologischer Untersuchung von Dr. M. GEIGER (Gerinnungsphysiologisches Labor, Kantonsspital Zürich) und nach der von uns aufgenommenen Anamnese.

Anamnese (nach unserem Fragebogen S. 32–33, zusammengestellt):

Erste Manifestation der Blutungsbereitschaft bei dem Probanden im Alter von 2¹/₂ Jahren: andauernde Blutung nach einer Mundschleimhautverletzung.

Bei Verletzungen kommen langandauernde Blutungen vor. 1932 wurde der Proband infolge einer anhaltenden Blutung aus einer kleinen Wunde am behaarten Kopf aus der Armee ausgemustert, nachdem bereits früher verschiedene Blutungserscheinungen (siehe weiter unten) im Dienst behandelt werden mußten.

Suffusionen treten oft nach geringen Traumata auf.

Der Proband erlitt mehrere schwere Muskelblutungen:

1921 Kniegelenk- und Weichteilblutung nach einer Oberschenkelkontusion (Akten Eidg. Militärversicherung, Anamnese). 1941 Haematom des re. Oberschenkels, in solchem Ausmaße, daß Amputation erwogen wurde (Akten der Eidg. Militärversicherung). 1942 Blutungstumor im Bereich der Streckseite des li. Oberschenkels mit periostaler Reaktion (Krankengeschichte, Kantonsspital Chur). 1945 Kontusion am re. Oberschenkel mit Haematom lateral im Quadriceps; 4 Wochen ganz, 1 Woche 50% Arbeitsunfähig (Krankengeschichte, Kantonsspital Chur). 1948 infolge eines heftigeren Absitzens auf einer Fensterbank bildete sich ein Bluterguß in der Tiefe der re. Glutäalmuskulatur mit Druck auf den Plexus lumbalis; bleibende Folgen: Sensibilitätsausfall im Bereich der Wurzeln L1–L4. Motorischer Ausfall der Quadricepsgruppe, der Adduktoren, teilweise des Iliopsoas. Betroffen insbesondere N. cruralis und N. obturatorius. Gang erschwert, Hinken nach rechts. Atrophie der Oberschenkelmuskulatur von 6–7 cm. Umfangdifferenz. Patellar- und Kremasterreflex nicht auslösbar (Krankengeschichte, Kantonsspital Chur). 1952 beim Holzen re. Bein angeschlagen, 8 Tage später Schweregefühl im Bein, 11 Tage nach der Kontusion mußte der Proband die Arbeit aussetzen. Es handelte sich um eine ausgedehnte Blutung im Bereiche der rechten Oberschenkelmuskulatur mit einer ausgeprägten periostalen Reaktion, stärker als 1942, im Sinne einer Pseudotumorbildung (Dr. MARX, und Krankengeschichte des Kantons-spitals Chur). 1955 Haematom im re. Handrücken mit anschließender Bildung einer Haemocyste auf der Höhe des Metacarpus IV, die sich in einigen Wochen resorbierte (Dr. MARX).

Blutungen aus dem Zahnfleisch kommen von Zeit zu Zeit vor. Im 8. Lebensjahr des Probanden hatte er eine fünftägige Blutung nach einer Zahnextraktion (HOESSLY-HAERLE, S. 357–358).

Nasenblutungen kommen oft vor, besonders bei Föhnwetter und bei Aufregung. 1956 hatte der Proband während 3 Monaten täglich sickernde Nasenblutungen von ca. 15 Min. Dauer.

Kniegelenkblutung 1921, anläßlich der obenerwähnten Oberschenkelkontusion. 1932 Hüftgelenk- und Kniegelenkblutung im Militärdienst, vor der Ausmusterung.

1945 Magenblutung nach einem Stoß in die Magengegend (Krankengeschichte, Kantonsspital Chur).

Keine Blutungen im Zentralnervensystem aufgetreten.

Beim Probanden wurden im Kantonsspital Chur mehrmals Blutuntersuchungen durchgeführt, deren wechselnde Ergebnisse hier aus den Krankengeschichten zusammengestellt sind:

Jahr	Blutungszeit	Gerinnungszeit (BÜRKER)	Thrombozytenzahl
1942	1' 30''	7' 45''	345 800
1948	2' 30''	9' 30''	
1946		24' 30''	
1950	22''	3' 46''	
1952	2' 15''	3' 20''	193 800

Die starken haemophilen Erscheinungen beim Probanden sind vielleicht zum Teil durch seine physische Betätigung und mangelnde Schonung zu erklären, wie dies aus der folgenden Mitteilung von Dr. MARX ersichtlich ist: «In der Freizeit geht G. (der Proband, Verf.) mit Vorliebe ins Holz, fuhrwerkt, usw. d.h. alle Beschäftigungen betreibt, die für ihn ein erhöhtes Risiko darstellen. Er läßt sich aber nicht davon abbringen, weil ihm das Freude macht.»

Die Abnahme der Blutungsbereitschaft mit dem Alter wurde von der Mutter des Probanden bereits HOESSLY-HAERLE (1930). S. 307. mitgeteilt. Auch nach Aussage des Probanden *sind die Blutungserscheinungen im Laufe der Jahre deutlich zurückgegangen*, besonders die Blutergüsse in die Oberschenkelmuskulatur.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 21. September 1956: Haemophilie B.

Literaturangaben: HOESSLY-HAERLE, S. 307, 357–358; Pianta, S. 167 bis 169; FONTO, S. 81, Zeilen 29–33.

B N. 485: Anna Barbara G., von Safien, geb. 1913, lebt in Chur (E. Chur), kopuliert 1939 mit B N. 484 Hans N., von Lutzenberg, App., geb. 1914, lebt in Chur (E. Chur).

Die Probandin ist eine sichere Konduktorin, wie aus Tafel 6 ersichtlich.

PIANTA, S. 170, schreibt über sie: «Sie soll bei den Geburten verstärkt geblutet haben, obwohl sonst bei ihr absolut keine Blutungsneigungen auftraten. Auch die Menses sind normal.» Und dennoch führt sie Pianta, S. 195, in seiner «Zusammenstellung der Symptome erhöhter Blutungsbereitschaft bei den untersuchten Konduktoren» auf. Anhand

unserer Nachforschungen können wir jegliche Blutungsbereitschaft bei der Probandin mit Entschiedenheit ablehnen.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 19. September 1939: normale Gerinnungswerte.

Literaturangaben: PIANTA, S. 170, 195; FONIO, 24, 81.

B X. 490: Margret G., von Safien, geb. 1919, lebt in Flims (Z. Chur),
kopuliert 1941 mit B X. 489 Georg Gaudenz B., von Chur
und Tschierschen, geb. 1917, lebt in Flims (Z. Chur).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 21. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B X. 491: Josias G., von Safien, geb. 1920, lebt in Chur (Z. S.).

Bei HOESSLY-HAERLE, S. 307, 358, als Bluter bezeichnet. S. 358: «... J. G. (B X 491, Verf.) zeigt nur schwache Haemophilie. Im Alter von anderthalb Jahren blutete er einen Nachmittag lang aus einer kleinen Schnittwunde.»

Im Stammbaum der Arbeit HOESSLY-HAERLE wird der Proband als Bluter aufgeführt, mit dem Vermerk: «Mit 1½ Jahren profuse, stundenlang dauernde Blutung aus Schnittwunde am Finger.»

Nach den von uns angenommenen Richtlinien kann der Proband, lediglich auf Grund der obenbeschriebenen Blutung aus einer Schnittwunde, nicht als Bluter bezeichnet werden.

Unsere anamnестischen Nachforschungen ergaben keine Anhaltspunkte für die Blutungsbereitschaft des Probanden.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 21. September 1956: normale Gerinnungswerte.

Literaturangaben: HOESSLY-HAERLE, S. 307, 358.

B X. 493: Nina W., von Zeuthern, in Baden, Deutschland, geb. 1915,
lebt in Flums (K. Val. und Z. Scharans),
kopuliert 1946 mit B X. 692 Salomon M., von Scharans,
geb. 1914, lebt in Flums (Z. Scharans).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 19. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B X. 497: Ursula W., von Zeuthern, in Baden, Deutschland, geb. 1920,
lebt in Rodels (K. Val. und K. Rodels),
kopuliert 1946 mit B X. 496 Johann R., von Paspels, lebt
in Rodels (K. Rodels).

Die Probandin ist eine sichere Konduktorin, wie aus Tafel 6 ersichtlich.

PIANTA, S. 170, schreibt über sie: «Bei der Geburt des Knaben habe sie viel mehr Blut verloren als bei der des Mädchens. Die Menses hingegen sind vollständig normal.... Die Frau gibt an, daß bei ihr als Kind eine verstärkte Blutungsneigung bestanden habe, die sich in Form von starkem und oft auftretendem Nasenbluten geäußert habe. Auch weist die Patientin immer kleine Suffusionen am ganzen Körper auf, hauptsächlich an den Unterschenkeln. Diese treten auf als Folgen von leichten Traumen.» PIANTA, S. 195, 196, zählt die Probandin zu Konduktorinnen mit erhöhter Blutungsbereitschaft.

Im Laufe unserer Nachforschungen konnten wir die Aussagen von PIANTA über die Blutungsbereitschaft der Probandin nicht bestätigen. Die Probandin stammt aus einer Bluterfamilie, wo auf etwaige Blutungserscheinungen sehr geachtet wird, doch sind solche bei ihr von der Familie nicht beobachtet worden. Auch sie selbst nimmt nicht an, Blutungsneigung aufgewiesen zu haben; keine entsprechenden Zeichen konnten bei unserer Untersuchung festgestellt werden. Die von PIANTA erwähnten Suffusionen an den Unterschenkeln treten nur nach entsprechend starken Traumata auf.

Nach den von uns angenommenen Richtlinien können wir die Probandin nicht als Konduktorin mit Blutungsbereitschaft bezeichnen.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 21. September 1956: normale Gerinnungswerte.

Literaturangaben: PIANTA, S. 170, 195, 196; FONIO, S. 24, 81.

B X. 531: (auch A X. 73): Christian G., von Versam, geb. 1898,
† 1931 (Z. Ve.), kopuliert 1927 mit B X. 532 (auch A X. 74) Elsbeth H.,
von Safien, geb. 1901 (P. v. S.), lebt in Versam.

Bei HOESSLY-HAERLE, S. 347, Zeile 23 ff. unter «rudimentären Blutern» aufgeführt: «Der noch lebende C. G. (B X. 531, Verf.) bekam ca. 24 Stunden nach einer Zahnextraktion von normalem Verlauf plötzlich eine profuse Blutung aus der Zahnwunde, die nur mit ärztlicher Hilfe gestillt werden konnte.»

Die Frau und die drei Söhne des Propositus sind uns seit 1934 als Patienten bekannt; nach ihren Angaben, die wir als zuverlässig bezeichnen können, hat der Propositus außer der von HOESSLY-HAERLE beschriebenen Blutung nach Zahnextraktion an keinen anderen Blutungen gelitten und auch sonst keine Blutungsbereitschaft aufgewiesen. Somit kann der Propositus B X. 531 nach den von uns angenommenen Richtlinien nicht als «rudimentärer Bluter» bezeichnet werden.

Literaturangaben: HOESSLY-HAERLE, S. 347, Zeile 23 ff. bis S. 348, S. 358, Zeile 21 ff.

B XI. 449: Jakob C., von Ricin, geb. 1933, lebt in Riein (Z. Riein).
Der Proband wurde als Sohn einer möglichen Konduktorin (vgl. Tafel 6) untersucht.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 23. Oktober 1957: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B XI. 450: Anna Margret C., von Riein, geb. 1935, lebt in Riein (Z. Riein). Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 17. November 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B XI. 458: Christian H., von Ilanz, geb. 1947, lebt in Ilanz (Z. Ilanz).

Bluter: nach Diagnose der behandelnden Ärzte Dr. J. BUNDI, Ilanz, und Dr. B. CATHOMAS, Spital Ilanz, nach gerinnungsphysiologischer Untersuchung von Dr. M. GEIGER (Gerinnungsphysiologisches Labor, Kantonsspital Zürich) und nach der von uns aufgenommenen Anamnese.

Anamnese (nach unserem Fragebogen, S. 32–33, zusammengestellt):

1953 anlässlich einer Schwellung am Unterschenkel erstmals Haemophilie diagnostiziert (Dr. BUNDI), jedoch auch schon vor 1953 mehrmals Haematome und Gelenkergüsse; genaueres Datum der ersten Manifestation ist nicht eruierbar.

Bei kleinen Verletzungen steht die Blutung relativ rasch, bei größeren lange Nachblutungen (Dr. B. CATHOMAS). 1953 Quetschung an re. Backe mit perforierender Verletzung, darauf folgende Blutung dauerte 8 Tage, trotz angewendeten Coagulantien und Tamponade; anschließende Haemoglobinnormmessung ergab 52%.

Große Suffusionen kommen oft vor.

1954 Haematom am rechten Unterschenkel.

1955 nach Extraktion des 6. Molars li. unten, trotz Tamponade, eine 3 Tage dauernde Nachblutung, die erst auf Tamponade mit Sorbacel stand. Anschließend Infusion wegen Exsiccose. Haemoglobin 50%. Blutungszeit: 2', Gerinnungszeit (BÜRKER) 4'. 2 Monate später erneut starke Blutung nach Zahnextraktion.

Nasenblutungen kommen selten vor, können durch Tamponade mit blutstillender Watte (Eisenchlorid-Watte) in ca. 1/2 Stunde zum Stehen gebracht werden.

Gelenkblutungen vor 1953 aufgetreten (vgl. oben); genaues Datum nicht eruierbar.

Viscerale Blutungen und Blutungen in das Zentralnervensystem sind nicht vorgekommen.

Die Blutungsbereitschaft ist im Frühling erhöht.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 26. März 1957: Haemophilie B.

Literaturangaben: nicht beschrieben.

B XI. 462: Irma S., von Kästris, geb. 1935, lebt in Ilanz (Z. Kästris).
Die Probandin ist eine sichere Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 16. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B XI. 463: Rosmarie K., von Sarmenstorf, AG, geb 1941, lebt in Lenzburg (E. Lenzburg).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 16. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B XI. 464: Erika K., von Sarmenstorf, AG, geb. 1943, lebt in Lenzburg (E. Lenzburg).

gleich wie bei B XI. 463

B XI. 465: Margrit K., von Sarmenstorf, AG, geb. 1945, lebt in Lenzburg (E. Lenzburg).

gleich wie bei B XI. 463.

B XI. 466: Silvio K., von Sarmenstorf, AG, geb. 1946, lebt in Lenzburg (E. Lenzburg).

Bluter: Nach Pianta, S. 177, nach gerinnungsphysiologischer Untersuchung Dr. M. Geiger (Gerinnungsphysiologisches Labor, Kantonsspital Zürich) und nach der von uns aufgenommenen Anamnese:

Anamnese (nach unserem Fragebogen S. 32–33, zusammengestellt):

Erste Manifestation der Blutungsbereitschaft bei dem Probanden im Alter von 2 Jahren: 3 Tage andauernde Blutung nach einer Ritzverletzung an der oberen Gingiva, die erst im Spital durch Bluttransfusionen gestillt werden konnte, Haemoglobin bis auf 37% gesunken.

Nach Verletzungen verlängerte Blutungen, die jedoch relativ rasch gestillt werden können.

Große Suffusionen treten oft auf, auch nach relativ leichten Traumata. Einmal ist der ganze Unterarm unterlaufen gewesen.

Blutungen in die Weichteile wurden nicht beobachtet.

Blutungen aus der Gingiva traten erstmals, wie oben erwähnt, im Alter von 2 Jahren auf. 1950 blutete der Proband 4 Tage lang nach einem Schlag auf die vordere, obere Gingiva. Die Blutung konnte erst im Spital durch eine Bluttransfusion gestillt werden, Haemoglobin bis auf 55% ge-

sunken. Der Proband blutet von Zeit zu Zeit anhaltend nach geringen Verletzungen am Zahnfleisch. Nach einer Stockzahnextraktion im 5. Lebensjahr mußte der Proband infolge Blutung 10 Tage in Spitalpflege verbleiben.

Anhaltende Nasenblutungen sind einige Male aufgetreten.

Gelenkblutungen sind seit Schulbeginn im 7. Lebensjahr des öfteren im li. Ellbogen und im li. Fußgelenk vorgekommen, ausgelöst durch Spiel und Sport. Die Schwellung dauert jeweils mehrere Wochen lang. Das klinische Bild der Blutungserscheinungen wird durch die Gelenkblutungen dominiert.

Es sind keine visceralen Blutungen und keine Blutungen im Zentralnervensystem aufgetreten.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 15. September 1956: Haemophilie B.

Literaturangaben: PIANA. S. 177; FONIO. S. 82. Zeilen 24–28.

B XI. 472: Brusi M., geb. in den Vereinigten Staaten um 1949, lebt in Greenwood, Wisconsin (Mitteilung von B IX. 322 Anna Katharina B.-H., Großtante des Probanden, vgl. auch bei B. IX. 323).

Bluter: nach den uns von der Großtante des Probanden (vgl. oben) mitgeteilten Angaben. Der Proband bekommt oft Nasenbluten, Haematome und Suffusionen.

Literaturangaben: nicht beschrieben.

B XI. 478: Ruth Maria G., von Safien, geb. 1938, lebt in Chur (Z. S.). Die Probandin ist eine sichere Konduktorin, wie aus Tafel 6 ersichtlich. Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 19. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B IX. 479: Margrit Barbara G., von Safien, geb. 1941, lebt in Chur (Z. S.) gleich wie bei B XI. 478, jedoch gerinnungsphysiologische Untersuchung am 28. September 1956.

B XI. 480: Johann Martin G., von Safien, geb. 1943, lebt in Chur (Z. S.). Der Proband ist der Sohn eines Bluters, wie aus Tafel 5 ersichtlich. Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 28. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B XI. 481: Georg Christian G., von Safien, geb. 1946, lebt in Chur (Z. S.).
gleich wie bei B XI. 480.

B XI. 482: Heidi Martina J., von Praden, geb. 1940, lebt in Chur
(E. Chur).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 21. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B XI. 483: Ursula Elisabeth J., von Praden, geb. 1942, lebt in Chur
(E. Chur)

gleich wie bei B XI. 482.

B XI. 484: Johann Luzi J., von Praden, geb. 1944, lebt in Chur (E. Chur).
Der Proband wurde als Sohn einer möglichen Konduktorin (vgl. Tafel 6)
untersucht.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 21. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B XI. 485: Reto Gaudenz J., von Praden, geb. 1951, lebt in Chur
(E. Chur).

gleich wie bei B XI. 484.

B XI. 488: Lorenz Christian N., von Lutzenberg, App., geb. 1943, lebt
in Chur (E. Chur).

Der Proband wurde untersucht als Sohn einer sicheren Konduktorin und
Bruder eines Bluters (vgl. Tafel 5).

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 19. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B XI. 489: Hans Peter N., von Lutzenberg, App., geb. 1945, lebt in Chur
(E. Chur).

Bluter: nach PIANTA, S. 169–170, nach gerinnungsphysiologischer Untersuchung von Dr. M. GEIGER (Gerinnungsphysiologisches Labor, Kantonsspital Zürich) und nach der von uns aufgenommenen Anamnese.

Anamnese (nach unserem Fragebogen S. 32–33, zusammengestellt):

Erste Manifestation der Blutungsbereitschaft bei dem Probanden im Alter von 2 Jahren: mehrstündige Blutung nach geringfügiger Verletzung

des äußeren Gehörganges anlässlich einer Ohrspülung bei Otitis media. Die Blutung konnte erst im Spital durch Bluttransfusion gestillt werden. Haemoglobin war auf 66% gesunken.

Bei Verletzungen steht die Blutung zuerst nach einer normal kurzen Zeit, dann beginnt eine sickernde Nachblutung, die mit Unterbrechungen stunden- und tagelang andauert. Schnittverletzungen heilen jedoch manchmal normal ab.

Suffusionen kommen häufig nach geringen Ursachen vor.

Blutungen in die Weichteile sind nach Anstoßen vorgekommen, die Rückbildungszeit der Haematome dauerte bis 3 Wochen.

Zahnfleischblutungen kommen oft vor, manchmal ohne nachweisbare Ursachen. Sie dauern mehrere Stunden an. Starke Blutungen beim Zahnwechsel.

Nasenblutungen treten oft auf, mit mehrstündiger Dauer.

Gelenkblutungen wurden nicht beobachtet.

Nach einem Fall wurde Blut im Stuhl (pechschwarzer Stuhl) beobachtet, vielleicht verschlucktes Blut aus einer gleichzeitig erfolgten Mund- und Nasenblutung. Sonst keine visceralen Blutungen beobachtet.

Blutungen im Zentralnervensystem nicht aufgetreten.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 28. September 1956: Haemophilie B.

Literaturangaben: PIANA, S. 169–170; FONIO, S. 81, Zeilen 34–38.

B XI. 490: Andreas N., von Lutzenberg, App., geb. 1947, lebt in Chur (E. Chur).
gleich wie bei B XI. 488.

B XI. 493: Ursula Barbara B., von Chur und Tschierschen, geb. 1942, lebt in Flims (Z. Chur).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich. Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 21. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B XI. 494: Katharina Elisabeth B., von Chur und Tschierschen, geb. 1946, lebt in Flims (Z. Chur).
gleich wie bei B XI. 493.

B XI. 495: Anna Martina B., von Chur und Tschierschen, geb. 1947, lebt in Flims (Z. Chur).
gleich wie bei B XI. 493.

B XI. 496: Susanna Lucretia B. von Chur und Tschierschen, geb. 1951, lebt in Flims (Z. Chur).

gleich wie bei B XI. 493.

B XI. 497: Nina M., von Scharans, geb. 1947, lebt in Flums (Z. Scharans).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 19. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B XI. 499: Salome M., von Scharans, geb. 1950, lebt in Flums (Z. Scharans).

gleich wie bei B XI. 497.

B XI. 505: Marius R., von Paspels, geb. 1948, lebt in Rodels (K. Rodels). **Bluter:** nach Diagnose der behandelnden Ärzte Dr. E. BONIFAZI. Thusis, und Dr. P. STEINER, Spital Thusis, nach gerinnungsphysiologischer Untersuchung von Dr. M. GEIGER (Gerinnungsphysiologisches Labor, Kantonsspital Zürich) und nach der von uns aufgenommenen Anamnese.

PIANTA beschreibt den Probanden S. 170–171, ohne ihn mit Sicherheit als Bluter zu bezeichnen.

Anamnese (nach unserem Fragebogen, S. 32–33, zusammengestellt):

Erste Manifestation der Blutungsbereitschaft bei dem Probanden im Alter von 1 Jahr: Rißwunde am Frenulum der Oberlippe infolge eines Falles, wobei nach dreitägigem blutungsfreiem Intervall eine profuse Nachblutung folgte, die trotz Vernähen der Wunde durch Dr. BONIFAZI 2 Wochen andauerte und erst im Spital nach einer Bluttransfusion stand. Haemoglobin sank damals auf 35^o/_o. 2 Tage nach der Transfusion von 150 ccm Blut fand man folgenden Laboratoriumsbefund (Krankengeschichte, Spital Thusis): Hb. 46^o/_o, Gerinnungszeit (BÜRKER) 3 Min., QUICK-Prothrombinkomplex 19 Sek. 100^o/_o. Nach 12 Tagen im Spital und erneuter Transfusion von 200 ccm Blut stieg das Haemoglobin auf 66^o/_o, worauf der Proband entlassen wurde. Er fiel am gleichen Tage erneut und begann aus der gleichen Stelle zu bluten. Haemoglobin am nächsten Tage 60^o/_o, der Proband wurde wieder ins Spital aufgenommen, wo erst 9 Tage später ein vollständiger Wundverschluß konstatiert werden konnte.

Bei der Spitalaufnahme wurde anamnestisch festgestellt (Krankengeschichte, Spital Thusis), daß der Proband im ersten Lebensjahr schon kleinere Bagatellverletzungen hatte, die jedoch nie länger als normal bluteten.

Die Mutter B X. 497 des Probanden sagt aus (vgl. auch Pianta, S. 170), daß sie bei ihm im Alter von 2 Monaten Blut im Urin beobachtete; eine ärztliche Untersuchung fand damals nicht statt.

Nach Verletzungen kommt es jedesmal zu andauernden, manchmal tagelangen Blutungen.

Suffusionen kommen sehr oft und nach geringen Ursachen vor.

Größere Muskelblutungen wurden nicht beobachtet, es traten jedoch mehrmals Beulen (Haematome) auf, welche mehrere Tage lang blau geblieben sind (vgl. weiter hinten bei B XI. 507).

1949 Zahnfleischblutungen, wie oben beschrieben. 1955 traumatisch bedingte profuse subgingivale und submuköse Blutung, Gingiva der Incisivi im Unterkiefer war durch ein Coagulum von den Zahnhälsen leicht abgehoben; die Blutung dauerte 5 Tage. Haemoglobin sank auf 77% bis Einlieferung ins Spital, wo die Blutung gestillt werden konnte. 1955 dreitägige Blutung beim Durchstoßen eines Stockzahnes. 1956 profuse Zahnfleischblutung aus einer Rißwunde in der Gingiva des Unterkiefers.

Nasenblutungen sind nicht vorgekommen.

Gelenkblutungen: Mai 1954, Haemarthros im re. Kniegelenk und im re. Fußgelenk. Oktober 1954, erneut Haemarthros im re. Fußgelenk. September 1955, Haemarthros im li. Kniegelenk und li. Fußgelenk, wobei die Gelenkblutungen mehrmals hintereinander aufgetreten sind.

Viscerale Blutungen wurden nicht beobachtet, außer dem oben erwähnten blutigen Harn im 2. Lebensmonat des Probanden.

Blutungen im Zentralnervensystem sind nicht vorgekommen.

Der Proband ist sehr lebhaft. Die Gelenkblutungen sind ohne sichtbare Folgen abgeheilt.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 13. August 1956: Haemophilie B mit 2,5% an Faktor IX (vgl. auch bei B XI. 507).

PIANTA, S. 170, schreibt über den Patienten (B XI. 505): «Der kleine Pat. gehört nicht mit Sicherheit zu den Haemophilen. Zu einer Gerinnungszeitmessung ist er noch zu klein und sie kann immer noch ausgeführt werden. Ich persönlich glaube jedoch an eine Haemophilie, denn im April 1949 mußte der kleine Patient zu einer Blutstillung ins Krankenhaus Thusis eingeliefert werden.»

Anhand der oben angegebenen Krankengeschichte und des Laboratoriumsbefundes können wir den Patienten *mit Sicherheit als Bluter bezeichnen*.

NB: Die Konkultorgroßmutter ist Ursulina G., B IX. 333, und nicht, wie bei Pianta, S. 171, ihre Schwester Barbara G., B IX. 331.

Literaturangaben: Pianta, S. 170–171.

B XI. 506: Ursula R., von Paspels, geb. 1949, lebt in Rodels (K. Rodels). Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 21. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

B XI. 507: Felix R., von Paspels, geb. 1952, lebt in Rodels (K. Rodels). **Bluter:** nach gerinnungsphysiologischer Untersuchung von Dr. M. GEIGER (Gerinnungsphysiologisches Labor, Kantonsspital Zürich).

Klinische Untersuchungen und die von uns aufgenommene Anamnese lassen keine Vermutung der Blutungsbereitschaft zu: der Proband hat manchmal Suffusionen, jedoch nicht abnormal häufig oder besonders groß. Nach Verletzungen normale Blutungszeit. Trotzdem der Proband aus einer Bluterfamilie stammt und einen Bluterbruder B XI. 505 hat (siehe oben), wodurch die Eltern auf eventuelle Blutungszeichen besonders achten, haben sie solche bei dem Probanden nie beobachtet.

Seine Mutter berichtet uns, daß bei dem Probanden die blauen Flecken (Suffusionen) selten und nur bei starkem Anstoßen, ähnlich wie bei seiner Schwester B XI. 506 und wie bei anderen nichthaemophilen Menschen, vorkommen. Im Gegensatz zu den Suffusionen und Haematomen bei dem klinisch manifest haemophilen Bruder B XI. 505, bei dem die Flecken mehrere Tage lang blau verbleiben, um sich dann als Zeichen der Besserung gelb zu verfärben, werden sie bei dem Probanden B XI. 507 schon nach 2 Tagen gelb.

Es scheint hier, daß die Mutter bei dem Bluter B XI. 505 das typische haemophile Nachbluten in die Haematome, welche das Fortdauern der blauen Verfärbung bedingt, richtig beobachtet hat. Bei den selten auftretenden Suffusionen des Probanden B XI. 507 müßte es sich somit nach Angaben der Mutter um normale traumatische Hautblutungen handeln, bei welchen keine Nachblutung in die Haut stattfindet und die Umbildung des Blutfarbstoffes in das gelbe Haematoidin bei der geringen Menge des in das Gewebe ausgetretenen Blutes rasch vor sich schreiten kann.

Die Aussagen der Probandenmutter betrachten wir als glaubhaft; sie zeugen von einer guten Beobachtungsgabe. Das *Fehlen jeglicher klinischer Zeichen der Haemophilie* konnte auch von uns festgestellt werden anlässlich unserer drei Untersuchungen des Probanden, die im Abstand von mehreren Monaten in den Jahren 1956 und 1957 stattgefunden haben.

Da der Proband Sohn einer sicheren Konduktorin ist (vgl. Tafel 6), wurde am 13. August 1956 eine gerinnungsphysiologische Untersuchung

(siehe S. 45–48) durchgeführt, die, mit 2,5% an Faktor IX, eindeutig pathologische Resultate lieferte mit der Diagnose Haemophilie B.

Literaturangaben: nicht beschrieben.

4. Nachfahrentafel Teil C

III. 10: Ursula WALTHER, von Tenna, geb. 1678, † 1757 (K.T. und K.S.),
kopuliert 1694 mit III. 9 Hans GARTMANN, von Tenna,
† 73jährig 1728 (K.T. und K.S.).

Die Proposita III. 10 wird von uns, wie auch schon von HOESSLY-HAERLE S. 342–343, als die Tochter des Stammelternpaares II. 2 und II. 3 und als Stammutter der Nachfahrentafel Teil C angesehen.

HOESSLI, S. 18, nimmt eine 1678 geborene und 1757 ledig verstorbene Ursula WALTHER an. Sie soll nach ihm nicht identisch sein mit der 1694 verehelichten Ursula WALTHER, der Stammutter einer der von ihm angenommenen zwei Bluterlinien. Es gelingt HOESSLI jedoch nicht, für diese von ihm angenommene Stammutter einer Bluterlinie das Geburts- und Todesdatum in den Kirchenbüchern zu finden. Wir konnten nun alle in den Kirchenbüchern Tenna und Safien in der Zeit von 1678–1757 vorkommenden Frauen des gleichen Namens nach dem Tauf-, Ehe- und Sterbedatum zwanglos einordnen: (siehe S. 144)

C IV. 24: Philipp (Flip) G., von Tenna, geb. 1697, † 1702 (K.T.).
Bluter: nach K.T. wörtlich: «Gestorben 1702, des Hans G. (III. 9) ehelicher Sohn, hat gelebt 5 Jahr, 3½ monat, hatt sich vast zu todt blütet».

Hier «vast» als mittelhochdeutsches Relikt im Safiental erhalten; «vast» oder «fast» bedeutete im frühen Mittelhochdeutschen etwa: ganz, vollständig, so daß «vast zu todt blütet» heißt: er hat sich vollständig zu Tode geblutet.

Literaturangaben: HOESSLI, S. 14, 18; HOESSLY-HAERLE, S. 361.

C IV. 25: Albrecht G., von Tenna, geb. 1699, † 1730 (K.T.)
kopuliert 1726 mit C IV. 26 Witfrau Magdalena TESTER,
von Tenna, geb. 1694, † ? (K.T.).

Bluter: nach K.T. «Des Hans G. (III. 9) selig, ehelicher Sohn, gestorben im 31. Jahr, nachdem ds Blut alleß von ihm geflossen».

Literaturangaben: HOESSLI, S. 14, 18; HOESSLY-HAERLE, S. 361.

Lauf- nummer	Stamm- baum- nummer	Taufregister	Eheregister	Totenregister
1	III. 10	K. T. 1678, Ursula WALTHER des (II. 2) Ammann Albrecht WALTHER	K. T. 1694, Ursula WALTHER kopuliert mit (III. 9) Hans GARTMANN	K. S.-Neukirch, 1757, Ursula WALTHER im 81. Jahre gestorben
2	B IV. 6	K. T. 1709, Ursula WALTHER des (C III. 7) Samuel WALTHER und (C III. 6) Maria JUON	K. T. 1732, Ursula WALTHER kopuliert mit (C IV. 5) Joos GARTMANN	K. T. 1739, Ursula WALTHER des (C IV. 5) Joos GARTMANN Ehefrau
3	B V. 33	K. T. 1751, Ursula WALTHER des (C IV. 12) Christian WALTHER und (C IV. 13) Anna SUTTER	—	K. T. 1754, Ursula WALTHER des (C IV. 12) Christian WALTHER und (C IV. 13) Anna SUTTER
4	B V. 35	K. T. 1755, Ursula WALTHER des (C IV. 12) Christian WALTHER und (C IV. 13) Anna SUTTER	—	K. T. 1757, Ursula WALTHER des (C IV. 12) Christian WALTHER und (C IV. 13) Anna SUTTER

Die unter 3 und 4 aufgeführten Mädchen sind zu spät geboren, um eine Verwechslung mit III. 10 zu gestatten und können auch anhand der Kirchenbuchangaben als im Kindesalter gestorben identifiziert werden. Auch die unter 2 aufgeführte Frau gehört schon zu der nächsten Generation und könnte nicht als die Stammutter der Bluterlinie angenommen werden, so daß nach den Personalangaben aus den Kirchenbüchern die unter 1 aufgeführte Ursula WALTHER als die Stammutter der Nachfahrentafel Teil C angesehen werden muß.

Der Einwand von HOESSLI, daß die Proposita im Sterberegister mit ihrem Mädchennamen WALTHER aufgeführt wurde und also als ledig verstorben gelten muß, ist nicht überzeugend, da in den alten Sterberegistern von Tenna, Safien und Versam die verheirateten Frauen in der Regel mit ihrem Mädchennamen eingetragen wurden. Der Vermerk mit wem sie verheiratet waren, ist nicht immer zu finden: vgl. auch die hier unter 2 aufgeführte Ursula WALTHER (B IV. 6). Endlich wird die Behauptung von HOESSLI über das 1694 zu junge Heiratsalter der 1678 geborenen Ursula durch die folgende Tabelle entkräftet, aus der das junge Heiratsalter mehrerer Frauen vom Safiental in der gleichen Zeitperiode ersichtlich ist.

Heiratsalter der Frauen III.–V. Generation aus der Nachfahrentafel der Bluter von Tenna

Die Tabelle erfaßt nur Ehen, bei welchen das Heiratsalter der Frau aus den Kirchenbüchern ersichtlich ist; zusätzlich ein Beispiel nicht aus der Nachfahrentafel.

Generation	Frauen über 20 Zahl der Ehen	Frauen unter 20, einzeln aufgeführt							
		Standort- nummer in der Nachfahren- tafel	Tauf- datum der Frau	Quelle	Heirats- datum	Quelle	Heirats- alter der Frau	Heirats- alter des Mannes	Bemerkungen
III.	1	III. 10	9. 3. 1678	K. T.	? 6. 1694	K. T.	16 J. 3 M.	39 J.	Propo- sita
IV.	9	A IV. 2	14. 10. 1722	K. S.- Platz	10. 4. 1739	K. S.- Platz	16 J. 6 M.	keine An- gabe	
		B IV. 11	27. 11. 1729	K. T.	4. 4. 1749	K. T.	19 J. 4 M.	30 J.	
		B IV. 13	? ? 1719	K. Ve. ¹⁾	? ? 1738	K. Ve. ¹⁾	ca. 19 J.	21 J.	
V.	13	A V. 2	9. 2. 1754	K. S.- Platz	26. 10. 1773	K. S.- Platz	19 J. 8 M.	32 J.	
		B V. 29	25. 3. 1741	K. Val.	26. 7. 1759	K. T.	18 J. 4 M.	43 J.	
		C V. 79	15. 10. 1738	K. T.	19. 5. 1758	K. T.	19 J. 6 M.	44 J.	
Extratafel 2. zu Nach- fahrentafel Teil C		Maria STÖCKLI Michel ZINSLI	1. 6. 1713	K. S.- Talkirch K. S.- Talkirch	23. 6. 1730	K. S.- Talkirch	17 J. 1 M.	21 od. 25 J.	
Beispiel nicht aus der Nach- fahrentafel		Maria JUON Christian JUON	25. 12. 1717	K. S.- Neukirch	21. 5. 1734	K. S.- Neukirch	16 J. 5 M.	22 J.	

¹ Das alte K. Ve. ist verloren gegangen, die Daten stammen von HOESSLY-HAERLE, welche das Buch noch einsehen konnte.

Die Identität der 1678 geborenen, 1694 verheirateten und 1757 verstorbenen Ursula WALTHER (III. 10) als Stammutter der Nachfahrentafel Teil C wird auch durch die Namengebung ihrer Kinder bestätigt, indem ihre älteste Tochter C IV. 23 Ursula nach ihrer Mutter II. 3 Ursula, geborene BUCHLI, und ihr zweiter Sohn C IV. 25 Albrecht nach ihrem Vater II. 2 Albrecht WALTHER getauft wurde, wie dies der zeitgenössische streng gehandhabte Brauch in Graubünden gewesen ist.

Literaturangaben: HOESSLI, S. 15, 18; HOESSLY-HAERLE, S. 341–342, 360.

C IV. 30: Hans G., von Tenna, geb. 1705, † 1711 (K.T.).

Bluter: nach K.T. wörtlich: «Gestorben 1711 nachdeme dz blut jhme alles ausgelofen ist»....

Literaturangaben: HOESSLI, S. 14, 18; HOESSLY-HAERLE, S. 361.

C V. 74: Christian BÜHLER, von Tenna, geb. 1729, † 1789 (K.T.),

kopuliert I° 1757 mit C V. 73 Anna WEIBEL, von Tenna,
geb. ?, † 1765 (K.T.)

kopuliert II° 1768 mit C V. 75 Anna BREHM, von Tenna.
geb. 1739, † 1810 (K.T.)

(siehe auch C V. 75).

Der Propositus kann als **Bluter** angenommen werden, da C IV. 24, C IV. 25, C IV. 30 (siehe dort) Brüder seiner Mutter C IV. 28 Barbara geborene G., nachgewiesenermaßen Bluter, und alle seine vier Töchter C VI. 114 Katharina, C VI. 116 Barbara, C VI. 118 Ursula und C VI. 121 Anna, Bluter-mütter gewesen sind. Auch kann bei den Vorfahren seiner zweiten Frau C V. 75 (siehe dort) in der Frauenlinie mütterlicherseits mit Berücksichtigung sämtlicher Geschwister kein Blutererbgang festgestellt werden.

Mit seiner ersten Frau C V. 73 hatte der Propositus nur einen Sohn, C VI. 111 Hans, der keine Nachkommen hinterließ.

Den angenommenen Richtlinien entsprechend konnte jedoch der Propositus C V. 74 in unserer Nachfahrentafel nicht als sicherer Bluter bezeichnet werden, da er im Gegensatz zu anderen uns bekannten Bluter-fällen seiner Zeitperiode weder bei den früheren Autoren noch in einem Kirchenbuchvermerk als Bluter bezeichnet wird. Es konnte jedoch auch ein Bluter aus dem Ende des 18. Jahrh. den Autoren des 19. Jahrh. entgangen sein und ebenfalls in den Kirchenbüchern unerwähnt bleiben (vgl. Kapitel: Erfassung der vor der Bestandesaufnahme 1952–1956 verstorbenen Bluter). *Somit kann mit großer Wahrscheinlichkeit angenommen werden, daß der Propositus C V. 74 ein Bluter gewesen ist* und die Vererbung der Haemophilie auf die Nachkommenschaft des Ehepaares durch ihn erfolgte. In den Beschreibungen wird er von uns als «mutmaßlicher Bluter» bezeichnet.

Literaturangaben: GRANDIDIER, S. 59. Zeile 14; HOESSLI, S. 19; HOESSLY-HAERLE, S. 361–362.

C V. 75: Anna BREHM, von Tenna, geb. 1739, † 1810 (K.T.),

kopuliert 1768 als zweite Frau mit C V. 74 Christian BÜHLER,
von Tenna, geb. 1729, † 1789 (K.T.), (siehe auch C V. 74).

Die Vorfahren von C V. 75 in der Frauenlinie mütterlicherseits mit Be-

EXTRATAFEL 2

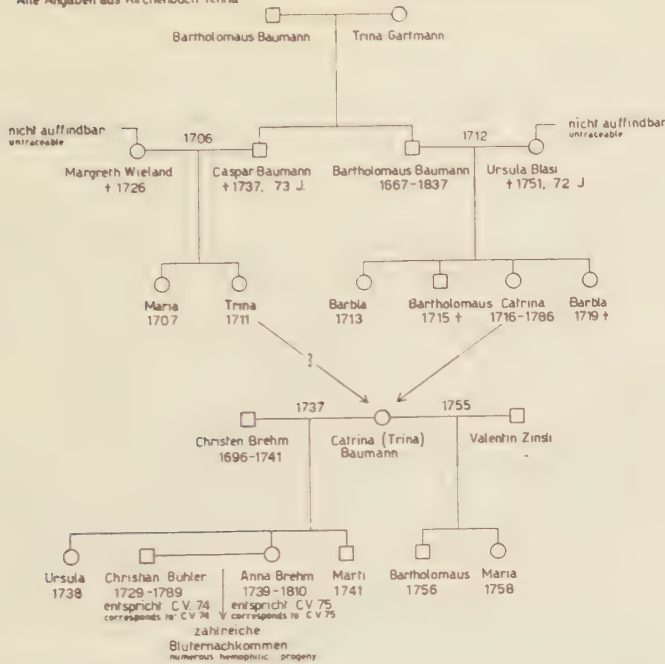
zu Nachfahrentafel Teil C

Alle Angaben aus Kirchenbuch Tenna

SUPPLEMENTARY TABLE 2

to part C of descendants' table

All data from parochial register of Tenna



rücksichtigung sämtlicher Geschwister sind in der Extratafel 2 zu Nachfahrentafel Teil C aufgeführt. Es wurde dadurch versucht, bei den Vorfahren der Proposita C V. 75 den haemophilen Erbgang festzustellen, der bei den Nachkommen aus ihrer Ehe mit C V. 74 (siehe dort) manifest wurde.

Infolge gleicher Namengebung (Catrina = Trina) konnte die Mutter der Proposita C V. 75 nicht mit Sicherheit unter zwei Kusinen Trina BAUMANN, geb. 1711, † ?, und Catrina BAUMANN, geb. 1716, † 1786, bestimmt werden, so daß beide Familienzweige zurückverfolgt wurden, wobei nach der bereits erwähnten traditionellen Namensgebung die Namen der ersten Tochter Ursula, geb. 1739, und des zweiten Sohnes Bartholomäus, geb. 1756, auf Catrina BAUMANN, Tochter von Bartholomäus und Ursula, hinweisen.

Wie aus der Extratafel ersichtlich, konnten keine Angaben über die Haemophilie bei den Vorfahren der Proposita C V. 75 ermittelt werden, was zwar an sich nicht verbindlich wäre, jedoch die Wahrscheinlichkeit erhöht, daß die Vererbung der Haemophilie auf die Nachkommenschaft des Ehepaares durch den Ehemann C V. 74 (siehe dort) erfolgte.

NB. Die Proposita C V. 75 Anna BREHM ist mit der Wilhelmine BRÄHM bei GRANDIDIER, S. 59, identisch, wie dies schon HOESSLI, S. 19, feststellte.

Literaturangaben: GRANDIDIER, S. 59, Zeile 13; HOESSLI, S. 19; HOESSLY-HAERLE, S. 361–362.

C VII. 184: siehe B, VI. 106.

C VII. 191: (auch B VI. 51): Peter B., von Tenna, geb. 1793, † 1831 (K.T.),
kopuliert 1815 mit C VII. 192 (auch B VI. 52) Barbara WALTHER, von Tenna, geb. 1793, † 1882 (K.T.).

Bluter: nach GRANDIDIER, S. 59: «Cathar. B. (C VI. 114). verheirathete C. (irrtümlicherweise anstelle von B., Verf.), hatte 2 Kinder. einen Sohn (C VIII. 191), der an einer enormen Blutgeschwulst starb, und eine Tochter (C VII. 190).»

Nach HOESSLI, S. 16, der seine Untersuchungen zu Lebzeiten der Frau (C VII. 192) des Probanden durchführte «Peter B., der uns zuerst auffällt. ist erwiesenermaßen ein Bluter...»

Literaturangaben: GRANDIDIER, S. 59, Zeile 17, wahrscheinlich auch S. 60, Zeilen 21–24; HOESSLI, S. 16, 19; HOESSLY-HAERLE, S. 362, 363.

C VII. 196: Domenicus RIZ à PORTA, von Guarda, geb. 1798, lebte noch 1814 nach K.T., † ? (K.T.).

C VII. 197: Christian RIZ à PORTA, von Guarda, geb. 1799, † ? (K.Ve.).

Einer dieser Brüder war **Bluter:** nach GRANDIDIER, S. 59 «Barbara B. (C VI. 116) heirathete den Pfarer Rh. (C VI. 115) und hatte 3 Kinder, wovon ein Sohn (C VII. 197 oder C VII. 196) sich früh verblutete, von den anderen ist nichts bekannt».

Nach HOESSLI, S. 21 «Barbla (C VI. 116) war mit Pfarrer RIZ à PORTA (CVI.115) verheirathet... Er (CVI.115) hatte zwei Söhne und eine Tochter; ein Sohn (CVII.197 oder CVII.196) verblutete sich ganz jung, vom anderen ist nichts bekannt geworden».

Aus den oben aufgeführten Quellenangaben ist ersichtlich, daß der Bluter «früh» gestorben ist, im Kirchenbuch Tenna finden wir aber noch 1814 eine Angabe über den damals 16jährigen CVII.196: «Er wurde unterrichtet und eingesegnet.» Somit besteht eine gewisse Wahrscheinlichkeit, daß der andere Bruder Christian der früh verstorbene Bluter ist; wir haben ihn auch als solchen in der Nachfahrentafel eingezeichnet.

NB. Aus den oben aufgeführten Quellenangaben scheint es, daß GRANDIDIER und HOESSLI der erstgeborene und im nächsten Jahre verstorbene Bruder C VII. 195, geb 1796, † 1797 an Blattern (K. T.), nicht bekannt war.

Literaturangaben: GRANDIDIER, S. 59, Zeile 23; HOESSLI, S. 21;
HOESSLY-HAERLE, S. 366.

C VII. 198: Alexander BUCHLI, von Tenna, geb. 1800, † 1813 (K.T.).
Bluter: nach GRANDIDIER, S. 60, Zeilen 24–26: «Einer seiner (CVII. 201, siehe dort) Brüder (also der Propositus CVII. 198, der nach K.T. ein Halbbruder des Vorgenannten gewesen ist; der andere Halbbruder ist CVII. 199, siehe dort, Verf.) starb im 13. Jahre, nachdem allgemeine Wassersucht der Blutung gefolgt war.»

Literaturangaben: GRANDIDIER, S. 59, Zeile 26, S. 60, Zeilen 24–26;
HOESSLI, S. 22, HOESSLY-HAERLE, S. 321, 367.

C VII. 199: Christian BUCHLI, von Tenna, geb. 1803, † 1831 (K.T.),
kopuliert 1830 mit C VII. 200 Anna Christina GREDIG, von
Safien, geb. 1807, † 1883 (K.T.).

Bluter: nach K.T. wörtlich: «Er starb nach einem fünf tägigen Krank-
lager zuzufolge eines heftigen Blutsturzes.»

Auch nach längerer Beschreibung durch den behandelnden Arzt Dr. F.
THORMANN, S. 340–343.

Katamnese nach THORMANN: Er behandelte den Propositus im Jahr
1829 wegen eines mannskopfgroßen Blutergusses im Skrotum. Der Erguß
trat plötzlich in der Nacht bei ruhiger Bettlage auf. «Als äußere Ursachen
derselben (Geschwulst, Verf.) wußte B. nichts anzugeben, als daß er drei
Tage zuvor von einer Kuh mit dem Fuße in die rechte Leistengegend ge-
schlagen wurde, jedoch so leicht, daß er bis jetzt nicht die mindesten
Schmerzen davon verspürte. Da mir das Entstehen der Haematocoele von
so geringfügiger Ursache fast unerklärlich schien, forschte ich den näheren
und entfernten Ursachen derselben tiefer nach, und nach langem Hin- und
Herfragen ergab sich endlich, daß B., wie alle Mannspersonen seiner Ver-
wandtschaft, große Neigung zu starken Blutflüssen besaßen, indem bei
diesen nach den kleinsten Verletzungen, z.B. nach Ritzen mit einer Nadel,
gewöhnlich am dritten Tage nachher, selbst in Fällen, wo diese schon wieder
geheilt waren, sich an der verletzt gewesenen Stelle ein blaues Bläschen
zeigte, welches bald zerplatzend kürzer oder länger hinfort beständig Blut
ergoß, so daß sich die Betreffenden beinahe verbluteten.» THORMANN be-
handelte den Propositus, worauf in einigen Wochen eine vollständige Re-
sorption eintrat. Der Autor berichtet ferner:

«Im Herbst 1832, drei Jahre nach der Haematocoele, zog sich B. eine
kleine Verletzung in der Nähe des Kniegelenkes zu, aus welcher nach etli-
chen Tagen, als B. zufällig von Hause entfernt war, eine so heftige Blutung

eintrat, daß sie ihm, bevor ich noch zu ihm gelangen konnte, schon das Leben geraubt hatte.»

Die Todesursache im K.T. «nach fünf Tagen Krankheitslager» kann mit dem Bericht von THORMANN, der damals in Chur praktizierte, gut in Einklang gebracht werden, da dieser durch Boten benachrichtigt werden mußte und so bei guten Wetterverhältnissen frühestens in zwei Tagen nach dem Unfall in das weitabgelegene Tenna gelangen konnte; auch wurde er wohl nicht sofort nach dem Unfall zugezogen.

NB. Nach K. T. ist der Propositus mit 28 Jahren gestorben, und nicht mit 23 wie bei THORMANN, S. 340, nicht mit 38 wie bei GRANDIDIER, S. 60, Zeilen 26–27, oder mit 33 wie bei HOESSLI, S. 22.

Literaturangaben: THORMANN, S. 340–343; GRANDIDIER, S. 59, Zeile 26, S. 60, Zeilen 26–27; HOESSLI, S. 22–23; HOESSLY-HAERLE, S. 320, 322, 367.

C VII. 201: (auch B VII. 104) Hans B., von Tenna, geb. 1812, † 1856 (Z.T.),

kopuliert 1840 mit C VII. 202 (auch B VII. 105) Katharina WALTHER, von Tenna, geb. 1820, † 1862 (Z.T.).

Bluter: nach GRANDIDIER, S. 59. Zeilen 26–27: «Ursula B. (C VI. 118)... aus zweiter Ehe 1 Sohn (C VII. 201) und 2 Töchter (C VII. 204, C VII. 205). Der Sohn ist Bluter.»

Ferner nach GRANDIDIER, S. 60, Beschreibung des Falles durch den behandelnden Arzt Dr. VIELI, wie folgt:

Katamnese nach VIELI: Der Propositus C VII. 201 «... kam öfters wegen Blutung in Behandlung, einmal wegen enormer Anschwellung des rechten Oberschenkels in Folge einer Contusion. Dieselbe dauerte mehrere Monate... Wenn B. sich einmal in den Finger schnitt, so erfolgte stets enorme Blutung».

NB. Nach Z. T. ist der Propositus 1856 gestorben und nicht 1862 wie bei HOESSLI, S. 24.

Im K. T. sind keine Angaben über die Todesursache oder Haemophilie des Propositus zu finden, wie dies HOESSLY-HAERLE im Textteil und im Stammbaum angibt; vermutlich liegt hier eine Verwechslung mit dem im Kirchenbuch vier Zeilen tiefer angeführten C VIII. 299 (siehe dort) mit gleichem Namen und Vornamen vor.

Literaturangaben: GRANDIDIER, S. 59, Zeile 27, S. 60; HOESSLI, S. 24; HOESSLY-HAERLE, S. 321, 367.

C VII. 208: Peter BÜHLER, von Tenna, geb. 1804, † 1808 (K.T.).

Bluter: nach GRANDIDIER, S. 59–60, «Anna B. (C VI. 121), verheirathet nach Masein; ein Sohn (der Propositus C VII. 208) von ihr starb früh an

Blutung». Nach HOESSLI, S. 26: «... diese (C. VI. 121) heirathete einen Johannes Bueler (C VI. 120) und hatte drei Kinder: Peter (der Propositus C VII. 208), Anna (C VII. 210) und Cillia (C VII. 212). Peter hat sich verblutet.»

HOESSLY-HAERLE, S. 367, 368, schreibt, daß sich der Propositus an einer kleinen Schnittwunde verblutet hat, nach Angaben seiner Nichte C VIII. 353, geb. 1846, † 1927 (Z. Masein).

Literaturangaben: GRANDIDIER, S. 59–60; HOESSLI, S. 26; HOESSLY-HAERLE, S. 367.

C VIII. 291: Joos BUCHLI, von Tenna, geb. 1810, † 1837 durch Selbstmord (K.T. und K. Chur).

Bluter: nach zeitgenössischen Zeugenaussagen bei HOESSLI, S. 19–20, welcher den nicht haemophilen Bruder C VIII. 296 Michael noch untersuchen konnte und nach VIELI, bei GRANDIDIER, S. 59, Zeilen 16–21, der ohne genaue Angaben über Gebrüder BUCHLI (siehe auch C VII. 293, C VIII. 297, C VIII. 299) spricht, von welchen ihm drei Bluter und ein Nichtbluter bekannt sind.

Literaturangaben: GRANDIDIER, S. 59, Zeilen 16–21; HOESSLI, S. 19 bis 20; HOESSLY-HAERLE, S. 362.

C VIII. 293: Peter BUCHLI, von Tenna, geb. 1815, † 1862 (K.T. und Z.T.).

Bluter: nach K.T. wörtlich: «... er war ein sogenannter Bluter»; auch nach zeitgenössischen Zeugenaussagen bei HOESSLI, S. 19–20, und nach GRANDIDIER wie bei C VIII. 291 (siehe dort).

Todesursache nach K.T. «wahrscheinlich Seitenstich», d.h. Pneumonie.
Literaturangaben: wie bei C VIII. 291 (siehe dort).

C VIII. 297: Abraham BUCHLI, von Tenna, geb. 1822, † 1830 (K.T. und Z.T.).

Bluter: nach K.T. wörtlich: «Er starb... vorzüglich an Gichtern, nachdem er vorher wegen einem kleinen Fall fast ganz ausgeblutet»; auch nach zeitgenössischen Zeugenaussagen bei HOESSLI, S. 19–20, und nach GRANDIDIER wie bei C VIII. 291 (siehe dort).

Literaturangaben: wie bei C VIII. 291 (siehe dort).

C VIII. 299: Hans BUCHLI, von Tenna, geb. 1828, † 1857 (K.T. und Z.T.).

Bluter: nach K.T. wörtlich: «Er starb an Blutentzündung einer Hüfte,

und nachmaliger großer Blutverlust durch die Nase. Der Verstorbene gehörte zu den hiesigen sogenannten Blutern»; auch nach Beschreibung bei GRANDIDIER, S. 60–61, angegeben vom behandelnden Arzt Dr. VIELI.

Katamnese nach VIELI: der Propositus «Soldat, 20 Jahre alt, wurde auf dem Marsche zur Musterung plötzlich und ohne sichtbare Veranlassung von einer ungeheuren Anschwellung des rechten Oberschenkels befallen, die das bei Sugillationen gewöhnliche Farbenspiel zeigte... Solche Anfälle will der Patient schon oft gehabt haben, sie stellten sich immer unerwartet und ohne Vorboten ein. Sobald der Anfall eintritt, wird er kraftlos, nach wenigen Stunden ist er bettlägerig und bewegungslos und hat heftige Schmerzen, meist Hüftgelenke, seltener in den Knien.»

NB. GRANDIDIER, S. 60, spricht von Johann B., es handelt sich aber nach K. T und Z. T. ohne Zweifel um den oben genannten C VIII. 299 Hans BUCHLI.

Literaturangaben: GRANDIDIER, S. 59, Zeilen 16–21 und S. 60–61; HOESSLI, S. 19–20; HOESSLY-HAERLE, S. 322, 363.

C VIII. 323: Christian OTTO, von Chur, geb. 1833, † 1889 (K. Chur und Z. Chur),

kopuliert 1862 mit C VIII. 324 Anna WEBER von Hinteregg, ZH, geb. 1838, † ? (K. Chur und Z. Chur).

Bluter: nach Angaben von HOESSLY-HAERLE, S. 306, 325–326, 366.

HOESSLY-HAERLE gelang es, den Propositus mit Christian O. zu identifizieren, der 1872 vom behandelnden Arzt A. CANTANI in Neapel beschrieben wurde. HOESSLY-HAERLE schreibt, die Notizen über den Propositus von dessen Schwager erhalten zu haben, welcher wohl C VIII. 315 Carl Johann Gottfried W., geb. 1827, † 1916 (K. Chur und Z. Chur) gewesen ist, da beide anderen Schwäger viel früher gestorben sind; C VIII. 315 war selbst Vater des Bluters C IX. 406 (siehe dort) und deshalb als Gewährsmann besonders geeignet.¹⁾

Katamnese nach CANTANI (bei HOESSLY-HAERLE) und HOESSLY-HAERLE: Erste Blutung im vierten Lebensjahr aus dem Zahnfleisch, seitdem im Kindesalter ständige Ekchymosen und kleinere Blutungen. Im siebenten Lebensjahr nach einer normalen Zahnextraktion eine drei Wochen andauernde Blutung, die erst durch eine Kompression mit Fingerdruck während 72 Stunden gestillt werden konnte. Ähnliche Blutung im

¹⁾ Auf unsere Anfrage hin teilt uns Frau Dr. G. T. HOESSLY-HAERLE mit, daß ihr diese Notizen durch die Familie W. überlassen wurden, und zwar erhielt sie diese von C X. 630, Arnold M.

Anhand der von uns eingesehenen Familienpapiere von C X. 627 können wir die katamnestischen Angaben über den Propositus C VIII. 323 bestätigen.

zehnten Lebensjahr nach Entfernung des Verbandes von einer Schnittwunde am Finger. Vom zehnten bis achtundzwanzigsten Lebensjahr keine Manifestationen der Blutungsbereitschaft außer zwei Blutungen bei Zahnextraktion. Im achtundzwanzigsten Lebensjahr spontane Haematurie während 30 Tagen; ein Jahr später intestinale Blutung und Haematurie, später keine haemophilen Beschwerden bis zum siebenunddreißigsten Lebensjahr, als sich der Patient auf einer Deutschlandreise in einen Finger schnitt, worauf trotz Verbandanlegung eine Blutung folgte, welche während der ganzen Reise München–Chur–Neapel fort dauerte. CANTANI behandelte den Propositus 1872 in Neapel wegen einer Hinterhauptwunde.

Der Patient verblutete 1889 in Chur infolge einer geringen Mundverletzung.

Literaturangaben: CANTANI nach HOESSLY-HAERLE, S. 326; HOESSLY-HAERLE, S. 306, 325–326, 366.

C VIII. 328: (auch B VIII. 248): Valentin H., von Tenna, geb. 1840, † 1891 (Z. T.)
kopuliert 1866 mit C VIII. 329 (auch B VIII. 249) Christina Barbara
JEHLI, von Versam, geb. 1840, † 1900 (Z. T.).

Entgegen der Annahme von HOESSLY-HAERLE, S. 348, 355, 467, kann der Propositus nicht als «rudimentärer Bluter» bezeichnet werden.

HOESSLY-HAERLE schreibt über diesen Fall, S. 348: «Meinen Bericht über die *kleinen* (kursiv von uns, Verf.) Blutungserscheinungen bei V. H. verdanke ich einem absolut glaubwürdigen noch lebenden Zeitgenossen des V. H. Möglicherweise hat die Mutter, die in ihrer eigenen Familie tödlich verlaufende Haemophiliefälle erlebte, diese *relativ ungefährlichen* (kursiv von uns, Verf.) Blutungen als normal angesehen oder aber hat sie, wie so viele Blutmütter, Stillschweigen (HOESSLI gegenüber, Verf.) darüber bewahrt.» Im Stammbaum der Arbeit von HOESSLY-HAERLE heißt es aber über den Propositus V. H.: «Soll einige Male fast verblutet sein.» Seine angeblichen Blutungen werden somit im Stammbaum als bedeutend und im Textteil der Arbeit als unbedeutend bezeichnet; im Textteil polemisiert aber HOESSLY-HAERLE mit HOESSLI, der jegliche Blutungsbereitschaft seines Zeitgenossen C VIII. 328 ausdrücklich verneint (siehe weiter unten). Dabei ist die Bestandesaufnahme von HOESSLY-HAERLE in den Jahren kurz vor 1930 durchgeführt worden, so daß die Angaben ihres Gewährsmannes 30 bis 40 Jahre zurückliegende Ereignisse betreffen und angesichts der entgegengesetzten zeitgenössischen Aussagen von HOESSLI wohl auf einem Irrtum beruhen müssen.

HOESSLI, S. 24–26, beschreibt ausführlich die Gebrüder H. C VIII. 328, C VIII. 330, C VIII. 332, C VIII. 334, C VIII. 337, C VIII. 339, C VIII. 340, C VIII. 342, und stellt u.a. fest: «Wie man sich leicht denken kann, habe ich die Nachforschungen über diese Familie mit doppelter Sorgfalt angestellt, doch habe ich niemals von Jemand gehört, daß die Söhne H. irgendwann geblutet hätten; zwei derselben (C VIII. 340, C VIII. 342) habe ich selbst gesehen und den einen genauer untersucht»; zur Zeit dieser Untersuchung war also der Propositus, ohne je Blutungsbereitschaft aufgewiesen zu haben, an 40 Jahre alt gewesen.

Auch VIELL, der die Gebrüder H. in den Kinderjahren des Propositus beschrieb, weiß bei GRANDIDIER, S. 59, Zeilen 28–29, nichts über Blutungsbereitschaft bei ihnen zu be-

richten; er stellt lediglich bei einem der Brüder eine Gelenkschwellung fest, ohne sich auf die causale Diagnose einzulassen.

HOESSLI, S. 25–26, findet diese Gelenkanschwellung ungefähr dreißig Jahre später bei C VIII. 332 Jodokus H., wieder und sagt darüber aus: «Es ist richtig, daß dieser ein steifes Knie hat (Ankylose); jedoch glaube ich aus den gelieferten Schilderungen schließen zu dürfen, daß dies die Folge einer scrophulösen Kniegelenkentzündung ist und in keiner Beziehung zur Haemophilie steht.»

Auf Grund der oben aufgeführten Tatsachen kann der Propositus C VIII. 328 weder als Bluter noch als «rudimentärer Bluter» bezeichnet werden.

Literaturangaben: GRANDIDIER, S. 59, Zeilen 28–29; HOESSLI, S. 24–26; HOESSLY-HAERLE, S. 348, 355, 467.

C VIII. 351: Johannes F., von Masein, geb. 1842, † 1857 (Z. Masein).

Bluter: nach HOESSLI, S. 26: «Johannes (C VIII. 351) und Peter (C VIII. 352, siehe unten) waren Bluter; der Eine erlitt von einer Kuh einen Stoß an den Unterkiefer, der, obschon er an sich keine bedenkliche Quetschung verursachte, doch zu fataler Blutung führte»: HOESSLY-HAERLE, S. 368, findet die obigen Angaben durch die Schwester C VIII. 353 des Propositus bestätigt.

Literaturangaben: HOESSLI, S. 26, HOESSLY-HAERLE, S. 368.

C VIII. 352: Peter F., von Masein, geb. 1844, † 1874 (Z. Masein).

Bluter: nach HOESSLI, S. 26: «Johannes (C VIII. 351, siehe oben) und Peter (C VIII. 352) waren Bluter; ... der andere (C VIII. 352) bekam ohne bekannte Veranlassung eine Darmblutung. Mein Collega Dr. Buol. behandelte den Fall. Die Blutung trotzte allen angewandten Mitteln und starb der Patient innert 4–5 Tagen.»

HOESSLY-HAERLE, S. 368, findet die obigen Angaben durch die Schwester C VIII. 353 des Propositus bestätigt.

Literaturangaben: HOESSLI, S. 26; HOESSLY-HAERLE, S. 368.

C IX. 378: Barbara F., von Masein, geb. 1850, † 1902 (Z. Masein)

kopuliert 1872 mit C IX. 377 Johannes G., von Masein, geb. 1840, † 1899 (Z. Masein).

PIANTA, S. 172, schreibt über die Proposita: «Von ihr weiß man nur, daß sie einige Zeit vor dem Tode starke uterine Blutungen hatte. Auch hatte sie oft Nasenblutungen und fiel des öfteren in Ohnmacht.» Auf Grund dieser Anamnese spricht PIANTA, S. 195, von einer «etwas auffälligen» Blutungstendenz der C IX. 378.

Die Proposita ist 50 Jahre vor den Untersuchungen von PIANTA gestorben. Sie lebte zur Zeit der Untersuchungen von VIELI und HOESSLI, die, wie wir es bereits gezeigt haben, keinen Fall von Blutungsbereitschaft bei Frauen feststellen konnten (vgl. Kapitel: Frage der haemophilen Blutungserscheinungen bei den Frauen aus dem Bluterstamm von Tenna). Auch unsere Nachforschungen, die fast gleichzeitig mit PIANTA durchgeführt wurden, gaben uns keine Handhabe, bei der Proposita eine Blutungsneigung anzunehmen.

Literaturangaben: PIANTA, S. 172, 195.

C IX. 385: Martin G., von Valendas, geb. 1847, † 1873 (Z. Val.).

Bluter: nach Bericht von Dr. CH. WALTHER bei HOESSLI, S. 17: «Ein Sohn (C IX. 385), der von jung auf bei jeder noch so geringen Verletzung die charakteristischen Anschwellungen der Bluter erlitt, wurde im 25. Jahre an einer Hand durch ein Beil verwundet und starb, nachdem wiederholt bedeutende Blutungen in Zwischenräumen von 3–4 Tagen eingetreten waren, nach 3 Monaten am Starrkrampf.»

HOESSLY-HAERLE, S. 365, findet die obigen Angaben durch den Bruder C IX. 391 des Propositus bestätigt.

Literaturangaben: HOESSLI, S. 17; HOESSLY-HAERLE, S. 365.

C IX. 393: Alexander G., von Valendas, geb. 1857, † 1865 (Z. Val.).

Bluter: nach Bericht von Dr. CH. WALTHER, bei HOESSLI, S. 17: «Ein anderer Sohn (C IX. 393) starb infolge einer unbedeutenden Verletzung in der Kniekehle nach 8 Tagen an Verblutung.»

HOESSLY-HAERLE, S. 365, findet die obigen Angaben durch den Bruder C IX. 391 des Propositus bestätigt.

Literaturangaben: HOESSLI, S. 17; HOESSLY-HAERLE, S. 365.

C IX. 397: Katharina Barbara G., von Valendas, geb. 1863, † 1934 (Z. Val.)

kopuliert 1893 mit C IX. 396 Johann B., von Valendas, geb. 1852, † 1925 (Z. Val.).

Entgegen der Annahme von HOESSLY-HAERLE, S. 349, kann die Proposita nicht als «Teilbluterin» bezeichnet werden, lediglich weil «... Schwester mehrerer Bluter, bekommt zeitweise, ohne nachweisbare Ursache, an den Armen bläuliche Flecken, aus deren Zentrum sich Blut ausdrücken lassen soll. Sonst keine Blutungserscheinungen, Geburten normal, Menses o. B.» Nach PIANTA, S. 172, Zeilen 5–6: «Von ihr (C IX. 397) sind keine erhöhten Blutungsbereitschaften bekannt, außer, daß sie einmal eine starke Magenblutung gehabt habe.»

Die Familie der Proposita gehört zu unserem Patientenkreis. Nachforschungen bei ihren Verwandten und Nachkommen geben uns keine Handhabe, bei ihr eine Blutungsbereitschaft anzunehmen. Diese wird auch durch die von HOESSLY-HAERLE angegebenen gelegentlichen Suffusionen, die der Familie nicht aufgefallen sind, ebensowenig bewiesen, wie durch die einmalige Magenblutung, die von PIANTA erwähnt wird.

Nach den von uns angenommenen Richtlinien kann die Proposita nicht als «Teilbluterin» bezeichnet werden.

Literaturangaben: HOESSLY-HAERLE, S. 349, 365; PIANTA, S. 172.

C IX. 398: Abraham G., von Valendas, geb. 1865, † 1881 (Z. Val.).

Bluter: nach HOESSLY-HAERLE, S. 365, laut Aussagen von C IX. 391 (auch B VIII. 257) Peter G., Bruder des Propositus, jedoch ohne nähere Angaben. Der erwähnte C IX. 391, geb. 1855, † 1930 (Z. Val.), war selbst

Großvater von zwei Blutern B X. 478 und B X. 482. und deshalb als Gewährsmann besonders geeignet.

HOESSLI schreibt S. 17, laut Aussage des Arztes Dr. CH. WALTHER: «Vier Kinder (C IX. 389, C IX. 391, C IX. 397, C IX. 398, Verf.) sind noch am Leben und an diesen haben sich keine Spuren des Leidens gezeigt.» Der Propositus war aber zur Zeit des Berichtes höchstens 13 Jahre alt und vom berichtenden Arzt vielleicht längere Zeit nicht mehr gesehen worden; seine Blutungsbereitschaft konnte sich möglicherweise noch nicht, oder noch nicht besonders stark manifestiert haben, so daß sie in dem eher allgemein gehaltenen Bericht des Arztes an HOESSLI nicht erwähnt wurde.

Literaturangaben: HOESSLI. S. 17, Zeilen 6–8; HOESSLY-HAERLE, S. 365.

C IX. 406: Carl Bernhard W., von Chur, geb. 1856, † 1898 (Z. Chur).
kopuliert 1882 mit C IX. 407 Viktoria Alexandrina SECCHI,
von Zuoz, geb. 1860, † ? (Z. Chur).

Bluter: nach HOESSLY-HAERLE, S. 366: «Carl (C IX. 406) litt, nach Aussagen seines inzwischen verstorbenen Vaters, an schwer stillbaren Blutungen nach geringen Verletzungen und an multiplen Haematomen. Er starb 1898, 42jährig, nach plötzlichem Erbrechen großer Massen dünnflüssigen Blutes.»

Nach den von uns eingesehenen Familienpapieren von C X. 627 (siehe auch bei C X. 630) traten bei dem Propositus (C IX. 406) schon im Knabenalter häufige Suffusionen und Haematome auf.

Der erwähnte Vater des Propositus ist C VIII. 316 Carl Johann Gottfried W., geb. 1827, † 1916, der also mehrere Jahre vor den Untersuchungen von HOESSLY-HAERLE verstorben war. Auf unsere diesbezügliche Anfrage teilt uns Frau Dr. G. T. HOESSLY-HAERLE brieflich mit, daß es sich um einen Druckfehler handelt: «Statt Vaters' sollte es heißen: Aussagen seines inzwischen verstorbenen Schwagers', des Mannes der Lina W.» Der Gewährsmann wäre danach C IX. 412 Caspar Arnold M., geb. 1893, gewesen, der zwar erst 1945 gestorben ist, also zur Zeit der Veröffentlichung von HOESSLY-HAERLE noch nicht als «inzwischen verstorbenen» bezeichnet werden konnte. Doch wurden uns die Angaben von HOESSLY-HAERLE über den Propositus C IX. 406 auch durch den Sohn C X. 627 Otto M., des erwähnten Schwagers C IX. 412 Caspar Arnold M. bestätigt.

Literaturangaben: HOESSLY-HAERLE, S. 366.

C IX. 413: Lina Nanette W., von Chur, geb. 1860, † 1908 (Z. Zürich)
kopuliert 1893 mit C IX. 412 Caspar Arnold M., von Zürich, geb. 1868,
† 1945 (Z. Zürich).

Nach HOESSLY-HAERLE, S. 367: «... Frau Lina M.-W. (C IX. 413) ist die rudimentäre Teilbluterin, die an zahlreichen extramensuellen und Lungenblutungen litt.»

Unsere Angaben über die Proposita verdanken wir ihrem Sohn C X. 627 Otto M., geb. 1895, der sich gut erinnern kann, daß seine Mutter an Lungenblutungen litt. Es

handelte sich um Bluterbrechen, wobei nach Aussage der behandelnden Ärzte das Blut aus der Lunge kam.

Unser Gewährsmann C X. 627 überließ uns Aufzeichnungen seines Vaters C IX. 412, der eine genaue Krankengeschichte seines Blutersohnes C X. 630 Arnold M. in den Jahren 1901–1921 führte und sie mit einer Familienanamnese versehen hat. Wir lesen dort: «Die Mutter (Proposita C IX. 413, Verf.) des kleinen Arnold (C X. 630, Verf.) hatte oft genitale Blutungen („fréquentes pertes du sang, surtout par des époques irrégulières“), sie starb an Tuberkulose am 29. Juni 1908, nach häufigen starken Lungenblutungen während ihren zwei letzten Lebensjahren» (aus dem Französischen übersetzt, Verf.). Trotzdem HOESSLY-HAERLE (vgl. S. 328 und 366) diese Aufzeichnungen des C IX. 412 ebenfalls benützt hat, erwähnt sie die Tuberkulose der Proposita überhaupt nicht, gleich wie bereits bei dem ebenfalls an Haemophytisie verstorbenen B IX. 308 (siehe dort). In diesen beiden Fällen wurde von HOESSLY-HAERLE die offensichtliche Diagnose und der Grund der Lungenblutungen nicht angegeben und letztere als Zeichen einer Blutungsbereitschaft bei einem «rudimentären Bluter» (B IX. 308) bzw. einer «rudimentären Bluterin» (Proposita) ausgelegt.

Es ist anzunehmen, daß in einer Familie, wo die Blutungserscheinungen im nahen und auch im entfernten Verwandtenkreis so sehr beachtet worden sind, eine Blutungsneigung der Proposita, Ehefrau des 1945 verstorbenen C IX. 412 und Mutter unseres Gewährsmannes, sicherlich auch bemerkt worden wäre. Unser Gewährsmann versichert uns jedoch, daß er selbst keine haemophilen Blutungserscheinungen bei seiner Mutter beobachten konnte; auch hat sich sein Vater, welcher an der Haemophilie in der Familie sehr interessiert war, ihm gegenüber nie in diesem Sinne geäußert.

In Anbetracht der sehr kompetenten Aussagen unseres Gewährsmannes C X. 627 über die Haemophiliefälle in seiner Familie besteht kein Grund, an seinen hier wiedergegebenen Angaben zu zweifeln, besonders da auch HOESSLY-HAERLE über die angebliche Blutungsbereitschaft der Proposita nur aus Zeugenaussagen berichtet und bereits in mehreren anderen Fällen eine nachweislich *nicht* bestehende Blutungsbereitschaft bei Frauen angenommen hat (vgl. Kapitel: Frage der haemophilen Blutungserscheinungen bei den Frauen aus dem Bluterstamm von Tenna).

Nach den von uns angenommenen Richtlinien kann die Proposita nicht als «rudimentäre Teilbluterin» bezeichnet werden.

Literaturangaben: HOESSLY-HAERLE, S. 349, Zeilen 25–26; S. 366–367.

C X. 597: Johann Mathias G., von Masein, geb. 1875, † 1899
(Z. Masein).

Bluter: nach HOESSLY-HAERLE, S. 364: «... M.G. (C X. 597) stirbt 1899 ledig an Verblutung aus einer leichten Stichverletzung am linken Oberarm, die er sich laut ärztlichem Bericht beim Schafeschlachten zuzog».

NB. Das Geburtsdatum des Propositus im Stammbaum bei HOESSLY-HAERLE ist irrtümlicherweise 1855.

Literaturangaben: HOESSLY-HAERLE, S. 364.

C X. 601: Menga G., von Masein, geb. 1883, lebt in Masein (Z. Masein),
kopuliert 1907 mit C X. 600 Luzius E., von Masein, geb. 1877,
† 1933 (Z. Masein).

Die Probandin ist eine sichere Konduktorin, wie aus Tafel 6 ersichtlich.

PIANTA, S. 172, schreibt über sie: «Die Geburten sind normal. Die Menses sind regelmässig, aber acht Tage dauernd und alle zwei Wochen auftretend. Außer kleinen seltenen Nasenblutungen zeigt die Patientin keine Blutungsneigung.» Auf Grund dieser Anamnese rechnet PIANTA, S. 195, die Probandin unter die Konduktorinnen mit «erhöhter Blutungsbereitschaft». Weder die Ergebnisse unserer Untersuchungen, noch die Nachforschungen bei den Angehörigen der Probandin geben uns eine Handhabe, bei ihr eine Blutungsbereitschaft anzunehmen.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 1. Oktober 1956: normale Gerinnungswerte.

Literaturangaben: PIANTA, S. 172, 195.

C X. 604: Arnold G., von Masein, geb. 1889. † 1941 (Z. Masein),
 kopuliert I° 1920 mit C X. 603 Elsbeth P., von Luzein,
 geb. 1893, † 1924 (Z. Masein)
 kopuliert II° 1928 mit C X. 605 Menga T., geb. 1894, lebt in
 Masein (Z. Masein).

Bluter: nach HOESSLY-HAERLE, S. 364: «... A. G. (C X. 604). ... ist ein typischer Bluter mit fast unstillbaren Blutungen nach geringfügigen Verletzungen, großen Haematomen, Gelenkschwellungen usw. ... Er ... steht unter regelmäßiger Kontrolle des Spitalarztes, der ihm alle drei Monate einen Aderlaß von 250–500 cm³ Blut macht, augenscheinlich mit bestem Erfolg. ... Die Gerinnungszeit des Blutes ist nach Angaben des behandelnden Arztes deutlich verzögert. Die genauen Werte konnte ich leider nicht erhalten.»

Aus der Krankengeschichte der Chirurg. Abt. des Kantonsspitals Chur erfahren wir, daß der Propositus im Oktober 1940 das Auftreten einer Geschwulst an der Außenseite des re. Oberschenkels bemerkte; ein ursächlicher Zusammenhang mit einem Trauma war nicht festzustellen. Der Propositus gab an, an gleicher Stelle früher einmal ein Haematom infolge eines Hufschlages gehabt zu haben. Die neuentstandene Geschwulst zeigte ursprünglich eine rein weiche Konsistenz, mit der Zeit bildeten sich an einigen Stellen Verhärtungen, sie war auf der Unterlage verschieblich und ganz schmerzlos. Da die Geschwulst bis August 1941 nicht verschwand, sondern sogar etwas an Größe zunahm, wurde eine Operation beschlossen. Man fand einen unregelmäßigen, weit in die Muskulatur verzweigten und zum Teil bis an den Knochen reichenden Tumor von stellenweise derber und stellenweise zystischer Konsistenz. Die Zysten enthielten schokoladefarbene breiige Flüssig-

keit. Die histologische Untersuchung des Operationspräparates ergab ein Resorptionsgranulom.

Während der Operation trat keine auffallend starke Blutung ein. Am Tage nach der Operation kam es zu einer Nachblutung, die in der Krankengeschichte nicht genauer beschrieben ist. 10 Tage nach der Operation Exitus an Tetanus.

Literaturangaben: HOESSLY-HAERLE, S. 364.

C X. 607: Anna G., von Masein, geb. 1891, lebt in Masein (Z. Zollikon), kopuliert 1917 mit C X. 606 Ernst B., von Zollikon ZH, geschieden (Z. Zollikon).

Die Probandin ist eine sichere Konduktorin, wie aus Tafel 6 ersichtlich.

PIANTA, S. 175, schreibt über sie: «Die Geburten verliefen normal, ohne ärztliche Hilfe und ohne daß das Blut in abnormal großer Menge geflossen wäre. Die Menses dauern acht Tage, sind aber vollständig regelmäßig. Die Pat. hat nie abnormale Nasenblutungen, Mundblutungen oder Zahnblutungen. Eine Operation am Ductus choledochus ist prognosenmäßig verlaufen.» Trotz dieser Anamnese rechnet PIANTA, S. 195, die Probandin unter die Konduktorinnen «mit erhöhter Blutungsbereitschaft», und zwar wegen ihrer achttägigen Menstruationsdauer.

Weder die Ergebnisse unserer Untersuchung noch die Nachforschungen bei den Angehörigen der Probandin geben uns eine Handhabe, bei ihr eine Blutungsbereitschaft anzunehmen.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 1. Oktober 1956: normale Gerinnungswerte.

Literaturangaben: PIANTA, S. 175, 195.

C X. 608: Christian D., von Scharans, geb. 1876, † 1905 (Z. Scharans). **Bluter:** nach HOESSLY-HAERLE, S. 363: «... Chr. D. (C X. 608) von S., stirbt 1905 im Spital zu Samaden, wo er wegen eines Blutergelenkes lag, an einer inneren Blutung nach einem heftigen Hustenstoß; er war ein typischer Bluter, wie der ärztliche Bericht aussagt (Dr. B.).»

Im Verlaufe unserer Nachforschungen gelang uns lediglich festzustellen, daß der untersuchende Arzt Dr. Oscar BERNHARD gewesen ist. Nähere katamnestische Angaben sind nicht mehr erhältlich.

Literaturangaben: HOESSLY-HAERLE, S. 363, 364.

C X. 610: Margreth B., von Valendas, geb. 1894, lebt in Chur (K. Val.), kopuliert 1921 mit C X. 609 Christian F., von St. Antönien, geb. 1888, lebt in Chur (K. Val.).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 2. Oktober 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C X. 612: Katharina B., von Valendas, geb. 1895, lebt in Versam (P. Z. Val.),
kopuliert 1918 mit C X. 611 Jakob B., von Versam, geb. 1882.
† 1933 (Z. Ve.).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 17. Juli 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C X. 614: (auch B X. 319) Barbara B., von Valendas, geb. 1898, lebt in Valendas (P. Z. Val.), kopuliert 1922 mit C X. 613 (auch B X. 318) Daniel C., von Valendas, geb. 1896, lebt in Valendas (P. Z. Val.).

Die Probandin ist eine sichere Konduktorin, wie aus den Tafeln 5 und 6 ersichtlich.

PIANTA, S. 171–172, schreibt über sie: «Es sind bei ihr starke Nasenblutungen in ihren Mädchenjahren vorgekommen. Mit 18 Jahren hatte sie im Sommer eine langandauernde Blutung bei einer Zahnextraktion. Bei einer Geburt hatte sie eine ziemlich starke Blutung, die aber ohne Stillung zum Stehen kam.» PIANTA, S. 195, rechnet die Probandin zu Konduktorinnen mit «erhöhter Blutungsbereitschaft».

Die Probandin ist uns seit Jahren als Patientin bekannt, ohne daß wir bei ihr eine Blutungstendenz beobachtet haben. Im übrigen verweisen wir auf die Überlegungen im Kapitel: Frage der haemophilen Blutungserscheinungen bei den Frauen aus dem Bluterstamm von Tenna.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 17. Juli 1956: normale Gerinnungswerte.

Literaturangaben: PIANTA, S. 171–172, 195; FONIO, S. 24 (Barbara, Fall 2, von Tenna).

C X. 629: Lina M., von Zürich, geb. 1897, lebt in Zürich (Z. Zürich).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 5 ersichtlich.

HOESSLY-HAERLE schreibt über die Probandin S. 366: «Seine (C X. 630) 1897 geborene Schwester L. hat nach Untersuchungen von Dr. WEIL eine leicht verzögerte Gerinnungszeit ...». Siehe auch Gerinnungszeitbestimmung durch Dr. WEIL am 25.1.1909: «leicht verzögert», spezieller Teil S. 162.

Gerinnungsphysiologische Untersuchungen (Gerinnungsphysiologisches Labor, Kantonsspital Zürich) (s. S. 45–48) am 24. Juli und 8. August 1957.

Resultate:

	24. 7.	7. 8. 1957
Quick	100%	100%
Prothrombinverbrauchstest	20%	23%
Rekalzifizierungszeit	95''	160''
Fibrinogen		300 mg%
Prothrombin		100%
Faktor V		65%
Faktor VII-Komplex		95%
Faktor VIII		normal
Faktor IX		100%
Stuart-Prowerfaktor		90%
Thromboplastingeneration		
a) mit Plasma		normal
b) mit Patientenserum		normal
c) Plasma + Serum vom Patienten		± normal
Thrombingeneration (Pitney und Dacie)		normal
Retraktion (Saemann)		
total		54% (normal)
zeitlicher Ablauf		normal
Thromboplastingenerationstest mit den isolierten Plättchen der Patientin (4mal gewaschen)		normal ohne Besonderheit
Thromboelastogramm		starke Pseudolyse nach 36'

Eine Erklärung für den hier vorliegenden abnormen Prothrombinverbrauch kann mit den heute zur Verfügung stehenden Untersuchungsmethoden nicht gegeben werden. Es ist deshalb nicht zu entscheiden, ob sich bei dieser möglichen Konduktorin das Haemophilie B-Gen als pathologischer Prothrombinverbrauch manifestiert. Für ausführlichere Angaben sei auf die Arbeit HUSER, MOOR-JANKOWSKI, TRUOG und GEIGER (1958) verwiesen.

Literaturangaben: HOESSLY-HAERLE, S. 366.

C X. 630: Arnold M., von Zürich, geb. 1901, † 1938 (Z. Zürich).

Bluter: erstmals beschrieben von HOESSLY-HAERLE, S. 307, 328, 366, anhand der von C IX. 412 Caspar Arnold M., Vater des Propositus, aufgeschriebenen Krankengeschichte. Diese wurde von dem Vater 1909 angelegt und bis 1921 geführt, wobei sie eine ausführliche Familienanamnese (vgl. C VIII. 323, C IX. 406, C IX. 413), sowie anamnestische Angaben über den Propositus seit seiner Geburt enthält.

Der Bruder C X. 627 des Propositus hat uns in entgegenkommender Weise diese Krankengeschichte, sowie auch weitere Papiere aus dem Familiennachlaß zur Einsichtnahme überlassen. Es ergibt sich daraus ein *lückenloses typisches Krankheitsbild aus den Jugendjahren des Propositus*, welches wir wegen seiner Vollständigkeit im Folgenden kurz zusammengefaßt wiedergeben. *Auffallend ist daran die zeitliche Abnahme der haemophilen Erscheinungen bis zu ihrem vollständigen Ausbleiben seit dem 20. Lebensjahr des Propositus*. Dieses wurde vom Propositus und seiner Familie als Heilung angesehen und der Behandlung mit Pferdeserum durch den Pariser Arzt Dr. P. Emile WEIL zugeschrieben, wenn auch der Arzt selbst, in seiner von uns eingesehenen Korrespondenz mit der Familie, nur von Besserung spricht und beifügt «On reste hémophilique, quand on l'est».

Unsere Wiedergabe der Krankengeschichte enthält die Daten aller Eintragungen als Beweis ihrer Kontinuität. Wir bringen jedoch nur Angaben, welche die haemophile Erkrankung des Propositus betreffen und beschränken uns bei den übrigen – meist über banale Erkrankungen und das Familienleben – lediglich auf das Datum mit dem Vermerk o.B. (= ohne Beobachtung über die Haemophilie).

Die Krankengeschichte beginnt mit allgemeinen Angaben über den Propositus aus der Zeit von 1901–1909.

Seit früher Kindheit hatte er Suffusionen nach geringsten Ursachen und klagte über Schmerzen (Gelenkschmerzen?), die als Rheumatismus behandelt wurden. Er hatte immer schlechte Zähne und beim Milchzahnwechsel begann er aus den Zähnen und aus dem Zahnfleisch zu bluten. Den ersten Verdacht der Haemophilie (bei Zahnbluten?) hatten die Eltern jedoch erst 1906 und begannen dann dem Kind regelmäßig bis 1908 verschiedene Medikamente zu geben, die wenig Erfolg gegen die Blutungen (nicht präzisiert) zeigten.

Die genaue Krankengeschichte beginnt am 22.1.1909 mit einem Besuch bei Dr. WEIL in Paris.

25.1.1909: Bei Dr. WEIL, Hopital St-Louis, mit dem Propositus, seinem Bruder C X. 627 Otto und seiner Schwester C X. 629 Lina. Gerinnungszeitbestimmung: Propositus: 3 Std. 15 Min.; C X. 629: leicht verzögert; C X. 627: normal. 27.1.09: o.B. 29.1.09: 1. Einspritzung 22 cc Weil'sches Pferdeserum. 29.–31.1.09: o.B. 1.2.09: um 9 Uhr 2 vordere Milchzähne gezogen, ohne zu bluten. Die Nachblutung begann um 15 Uhr, die Wunde wurde mit Diphterieresum tamponiert. Die Blutung wurde stärker um 21 Uhr und dauerte an, trotz ärztlicher Tamponade mit Serum. 2.2.09: blutet weiter, Tamponade mit Pferdeserum-Pulver, Arzt 2mal zugezogen.

3.2.09: großes Coagulum am Zahnfleisch vom Zahnarzt entfernt ohne zu bluten. 21 Uhr eine erneute Blutung. 4.2.09: am Tag keine Blutung, am Abend blutet der Pat. wieder, aber weniger. 5.2.09: Dr. WEIL entfernt ein kleines Coagulum mit dem Verband. 8.–13.2.09: Fieber und Ausschlag, Patient bettlägerig. 14.2.09: Besserung des allg. Zustandes. 21.2.09: o.B. 23.2.09: Blutet an gleicher Stelle der Gingiva. 4.3.09: idem. 4.–6.09: Zahnschmerzen oben links. 7.3.09: blutet stark an linker Gingiva. 8.3.09: idem, weniger stark. 9.–10.3.09: blutet weiter aber nur nachts. 17.–21.3.09: Schmerzen und starke Schwellung am li. Bein unterhalb des Knies. Arztbesuch. 23.3.09: Unterschenkel vom Knie bis zum Fuß schwarz und grün. Arztbesuch. 24.3.09: Schwarze Flecken am li. Bein und am Gesäß links. Dr. WEIL sagt dem Vater, daß der Patient auch früher nicht an Rheumatismus, sondern an Haemophilie krank war, und seine Beschwerden und Schmerzen, die als Rheumatismus behandelt wurden (Gelenkschmerzen? vgl. auch Anamnese durch den Vater vor 1909), in Wirklichkeit durch Haemophilie verursacht wurden. 25.3.09: Flecken am Bein weniger ausgeprägt. 26.3.09: 2. Einspritzung 20 cc Weil'sches Pferdeserum; der Pat. reagiert mit Fieber und Erbrechen. 27.3.09: Fieber 38°C. 29.3.09: Arztbesuch, o.B. 2.4.09: Urticaria. 3.4.09: o.B. 4.4.09: o.B. 5.–7.4.09: Gesicht und Augen geschwollen. 7.4.09: blutet in der Nacht infolge eines lockeren Zahnes unten. 8.4.09: Blutung steht mit Serumpulver. 10.–11.4.09: blutet wieder in der Nacht. 12.4.09: Zahn entfernt, blutet etwas, Blutung steht mit Serumpulver. 13.–15.4.09: Blutet ständig, am Morgen ein großes Gerinnsel. 16.4.09: Blutung steht. 17.4.09: Gerinnungszeitbestimmung von Dr. WEIL, Spital St-Louis: 1 St. 30 Min. 18.–26.4.09: o.B. 27.4.09: o.B. 28.4.–18.5.09: o.B. 18.5.09: blaue Flecken am li. Knie. 30.5.09: Vorderen Zahn verloren, blutet etwas, Serumpulver-Verband. 5.6.09: Schmerzen im re. Ellbogen. 21.7.09: 3. Einspritzung Weil'sches Pferdeserum, darauf 37°C. 22.7.09: Schmerzen nach der Spritze. 23.7.09: o.B. 24.–26.7.09: geschwollenes Knie, Urticaria. 28.7.09: Urticaria. 29.–31.7.09: idem. 2.–3.8.09: blutet stark an Stelle der Einspritzung (vom 21.7.09), Arztbesuch. 4.8.09: blutet weiter, Serumverband. 5.8.09: Blutentnahme durch Dr. WEIL aus der Armarterie li. und von der Fingerspitze, Gerinnungszeit: 15 Min. (keine Angabe ob am arteriellen Blut oder am Finger gemessen). 7.–9.8.09: blutet an der Einstichstelle. 10.8.09: idem, mit Entzündung; Arztbesuch, Verband. 11.–13.8.09: weiterer Verband, Entzündung persistiert. 14.8.09: keine Entzündung mehr, doch immer noch Gerinnsel. Der li. Arm vorne ist schwarz und grün. 15.–19.8.09: Gerinnsel verbleibt, Verband. 16.–19.8.09: medikamentöse Behandlung. 20.8.–16.11.09: es geht gut. 17.11.09: 4. Einspritzung Weil'sches Pferdeserum, am

Abend Erbrechen und Blutung (wohl aus der Einspritzstelle). 18.11.09: blutet nicht mehr. 19.11.09: o.B. 22.11.09: Urticaria. 24.11.09: idem. 25.11.09: o.B. 26.–27.11.09: Urticaria. 28.–29.11.09: re. Handgelenk geschwollen, Schmerzen im re. Kniegelenk. 11.–13.12.09: rechte Hand geschwollen. 15.–18.12.09: re. große Zehe geschwollen. Bettlägerig. 19.–23.12.09: bleibt liegen, Schmerzen lassen nach. 24.12.09: Besserung, nimmt Eisenpräparat. 28.12.09: leidet wieder an re. großer Zehe. Urticaria. 29.12.09: bleibt liegen. 30.12.09: Besserung. 31.12.09: o.B.

1.–12.1.1910: o.B. 22.–23.1.10: blutet aus einem kleinen Zahn unten links, Arztbesuch. Tamponade mit Serumpulver und mit Wasserstoffsuperoxyd. 24.–26.1.10: blutet weiter, Tamponade mit Diphtherie-Serum. 26.1.10: 5. Einspritzung Weil'sches Pferdeserum. Blutet nicht mehr vom Zahn. 27.1.10: nur wenig in der Nacht geblutet (keine nähere Angabe). 28.1.10: blutet nicht mehr. 31.1.10: Extraktion von 3 Zahnwurzeln ohne zu bluten, Verband mit Serumpulver. 9.2.10: o.B. 17.–18.2.10: o.B. 19.2.–3.4.10: o.B. 4.–6.4.10: Schmerzen im re. Oberschenkel. 16.–21.4.10: re. Ober- und Unterschenkel angeschwollen, Schmerzen. 22.4.10: 6. Einspritzung Weil'sches Pferdeserum. 24.4.10: o.B. 24.–30.4.10: o.B. 1.–12.5.10: o.B. 13.5.10: Gerinnungszeitbestimmung im Hopital St-Louis: 30 Min. 31.5.10: o.B. 4.6.10: o.B. 7.6.10: o.B. 8.6.10: Schmerzen am li. Arm in Schulternähe. 9.–13.6.10: Beule an der schmerzhaften Stelle am Arm. 14.–18.6.10: Beule bildet sich zurück, die Haut ist verfärbt («toutes les couleurs»). 23.7.10: re. Ohr mit Fingernagel verletzt, starke Blutung, die auf einen Verband sofort steht. 26.–31.7.10: blutet aus hohlem Zahn oben rechts, Verband mit Serumpulver, nimmt jeden Abend Serumpulver innerlich. 27.–29.7.10: Schmerzen im re. Oberschenkel. 1.8.10: in der Nacht nicht geblutet (also dauerte die Blutung aus dem hohlen Zahn bis an dieses Datum). 7. Einspritzung Weil'sches Pferdeserum. 2.–3.8.10: leidet unter Schmerzen nach der Spritze, mehr am Bein als an der Seite(?). 4.8.10: o.B. 5.–6.8.10: o.B. 7.8.10: o.B. 1.–2.9.10: blutet leicht aus einem Zahn. 15.9.10: o.B. 23.9.10: o.B. 7.–8.–30.9.10: o.B. 3.10.10: 8. Einspritzung des Weil'schen Pferdeserums. 4.–5.10.10: bettlägerig. Urticaria. 8.–13.10.10: 4mal beim Zahnarzt, 3 Zähne plombiert, ohne etwas Besonderes. 17.10.10: o.B. 6.11.10: o.B. 2.–3.12.10: starker Schnupfen, Nasenbluten. 4.–10.12.10: o.B. 11.12.10: o.B. 15.12.10: ein blauer Fleck am Arm. 16.12.10: 9. Einspritzung des Weil'schen Pferdeserums. 17.12.10: o.B. 18.12.10: Stichwunde nach Einspritzung etwas schwärzer als sonst. 19.–31.12.10: o.B.

1.–31.1.1911: o.B. 1.2.11: o.B. 17.2.11: 10. Einspritzung des Weil'schen Pferdeserums. 17.–18.2.11: Fieber und Erbrechen in der Nacht.

18.2.11: o.B. 19.2.11: o.B. 26.–27.2.11: blutet ziemlich stark aus einem Zahn. März 1911: o.B. April 1911: o.B. 1.–8.5.11: o.B. 10.5.11: 11. Einspritzung des Weil'schen Pferdeserums. 11.5.11: o.B. 16.5.11: adenoide Vegetationen vom Arzt konservativ behandelt. 25.–31.5.11: blauer Fleck am re. Arm, später auch am linken, Schmerzen. 11.6.11: 1. Molar fällt aus (Zahnwechsel), blutet 24 Std. 1.–5.7.11: o.B. 10.–11.7.11: o.B. 25.7.11: blutet kurz aus einem Zahn. 31.7.11: 12. Einspritzung des Weil'schen Pferdeserums, anschließend Fieber, Erbrechen. 1.8.11: o.B. August–September 1911: o.B. Oktober 1911: o.B. 1.11.11: Dr. WEIL im Spital Hotel Dieu entnimmt Blut aus dem Ohr und Arm, Gerinnungszeit: 20 Min. 8.11.11: o.B., der Arzt hat Schwierigkeiten, dem Pat. das Serum einzuspritzen («tellement énérvé qu'il est impossible faire piqure»), so daß Serumeinläufe verordnet werden, die dann vom 9.–12.11.11 einmal täglich gegeben wurden. 4.12.11: zieht sich der Pat. einen Zahn am Unterkiefer, blutet 3 Nächte nacheinander, wenn auch immer weniger. Blutet nicht am Tage. Serumpulververband. 8.–20.11.11: o.B. 28.11.–4.12.11: o.B. 11.12.11: o.B. 12.–31.12.11: o.B.

10.1.1912: Dr. WEIL verordnet allmonatlich 3 Serumeinläufe. 22.–25.1.12: 3 Serumeinläufe. 30.1.12: ein oberer Zahn wurde vom Vater gezogen, blutet nur sehr wenig, keine Nachblutung. 21.–22.2.12: blutet etwas am li. Ohr. 23.–25.2.12: 3 Serumeinläufe. 20.3.12: Blutunterlaufene Beule nach einem Schlag auf die Stirn. Die Beule verschwindet durch Massage nach 18 Tagen. 2.–3.4.12: Schmerzen am li. Knie, die von alleine vergehen. 1.–3.5.12: 3 Serumeinläufe. 10.–20.5.12: o.B. 3.–6.6.12: 3 Serumeinläufe. 24.7.12: Dr. WEIL bestimmt Blutungszeit an beiden Ohrläppchen: 3½ Min. Gerinnungszeit vom Blut aus der Armvene: 5 Min. 25.7.12: o.B. 26.–30.7.12: 3 Serumeinläufe. 6.9.12: o.B. 7.–11.9.12: 3 Serumeinläufe. 11.–13.10.12: 3 Serumeinläufe. 30.10.–1.11.12: li. Knie und Unterschenkel stark geschwollen, Schmerzen, Arztbesuch. 2.11.12: schlaflose Nacht, starke Schmerzen, Arztbesuch. 3.11.12: idem, geschwollen auch oberhalb des Knies. 4.11.12: idem, auf Verordnung von Dr. WEIL Serumeinlauf. 5.11.12: idem. 6.11.12: Schmerzen mehr in der Nacht als am Tage, der 3. verordnete Serumeinlauf wird gegeben. 7.11.12: idem. 8.11.12: Besserung, der 5. verordnete Serumeinlauf. 9.11.12: Geschwulst geht zurück. 10.11.12: der Pat. kann das Bein nicht beugen. 11.11.12: schlechte Nacht. Während des Anfalles wurde jeden Tag der Arzt zugezogen, er stellt fest: interartikuläre Blutung im li. Kniegelenk. 12.–14.11.12: Geschwulst geht zurück. 15.–27.11.12: langsame Besserung, der Arzt kommt jeden 2. Tag. Am 26. beginnt der Pat. zu gehen. 28.11.12: stationärer Zustand. 29.11.12: Dr. WEIL wird zugezogen. 30.11.12: Besserung. 13.–15.12.12: o.B.

17.12.12: Dr. WEIL bestimmt Blutungszeit am re. Ohr(läppchen): $7\frac{1}{2}$ Min., Gerinnungszeit vom Blut aus der Armvene: 22 Min. 22.12.12: der Pat. zieht sich selbst einen Zahn, blutet sehr wenig, nur einige Minuten.

7.1.1913: 13. Einspritzung des Weil'schen Pferdeserums. 18.–20.1.13: li. Mittelfinger geschwollen. 29.–31.1.13: li. Oberschenkel geschwollen nach einer ermüdenden Reise, Schmerzen. 25.2.13: o.B. März–April 1913: nichts Abnormales, der Pat. hat einen Zahn verloren, ohne zu bluten. 28.5.13: Pat. bricht sich einen Zahn und blutet etwas in der Nacht. Blutung steht mit Serumpulver. 29.–31.5.13: blutet noch etwas. 1.6.13: blutet nicht mehr. 2.6.13: o.B. 3.6.13: 14. Einspritzung des Weil'schen Pferdeserums. 4.6.13: o.B. 5.6.13: o.B. 6.6.13: o.B. 7.6.–20.9.13: o.B. 22.9.13: o.B. 23.9.13: o.B. 24.9.13: 15. Einspritzung des Weil'schen Pferdeserums, darauf etwas Fieber und Erbrechen. Oktober, November, Dezember 1913: o.B.

Januar 1914: o.B. Februar–Juli 1914: o.B. 5.–7.8.14: li. Fuß geschwollen ohne ihn verstaucht zu haben («il ne s'est pas louché»), Heilung durch Massagen. 5.–10.9.14: leidet sehr am gleichen Fuß, der stark geschwollen ist. Kann nicht schlafen. 24.9.14: Schmerzen am gleichen Fuß, aber nur einen $\frac{1}{2}$ Tag. 25.9.14: o.B. Oktober 1914: o.B. 24.11.14: o.B. 27.11.14: Schmerzen im li. Fuß, immer an der gleichen Stelle: Serumeinlauf.

1915: alle 3–4 Monate schwillt der linke Fuß an, Schmerzen, die Anfälle dauern 4–5 Tage. 1916: wie 1915. 1917: wie 1916.

1918: die Schmerzen am li. Fuß kommen immer seltener.

1919: 1–2mal Schmerzen am Fuß während 2–4 Tagen.

1920: keine Fußschmerzen mehr, auch keine Anschwellung. Nach einer Verstauchung des li. Fußes Schmerzen während 3–4 Tagen, sonst o.B.

19.2.1921: Besuch bei Dr. WEIL, welcher den Patient am 25.2.1921 in der Académie de Médecine vorstellt.

Am 20.2.1921 schreibt Dr. WEIL an den Vater des Pat. (Brief in den Familienpapieren):

«Blutanalyse von Arnold gibt ganz gute Resultate:

a) *Gerinnungszeit*: das aus der Vene entnommene Blut in vitro ohne Sedimentation in 15–20 Min. Nach einigen Stunden gute Retraktion des Gerinnsels. Am nächsten Tag kein Zerfallen des Gerinnsels. Normales, klares, gelbes Serum.

b) *experimentelle Blutungszeit*: 2 Minuten (normal).

Schlußfolgerung: ich betrachte Arnold als geheilt, eine weitere Serumbehandlung ist nicht nötig. In einem Jahr soll man eine neue Blutanalyse durchführen.»

In einem späteren Brief schreibt der Arzt an den Vater des Pat. den eingangs erwähnten Satz: «man bleibt ein Bluter, wenn man als solcher geboren wurde».

HOESSLY-HAERLE hat den Propositus 1928 gesehen, was auch aus den Familienpapieren ersichtlich ist. Sie schreibt über ihn, S. 328: «Der jetzt ca. 29jährige Mann hat seit dem 21. Jahre keine Seruminjektion mehr nötig gehabt. Zahn- und Gelenkblutungen sind in den letzten Jahren fast (fast wird von HOESSLY-HAERLE nicht näher präzisiert, Verf.) vollständig verschwunden. In Anbetracht dieses ‚geheilten Zustandes‘ konnte ich ihn auch nicht untersuchen.»

Wir haben die Krankengeschichte des Propositus ausführlich mit seinem Bruder C X. 627 Otto M., geb. 1895, besprochen. Dieser, ein gebildeter Mann, der über die Haemophilie in der Familie gut Bescheid weiß, bestätigte uns aus seinen eigenen Erinnerungen die Eintragungen der hier wiedergegebenen Krankengeschichte. Anhand unseres Fragebogens (S. 32–33) sagt er aus, daß der Propositus C X. 630 seit seinem 20. Lebensjahr an gar keinen Blutungserscheinungen litt. Auch hat er nie einen Arzt zuziehen müssen. Als Todesursache des Propositus gibt unser Gewährsmann an: «Hirnblutung (Hirnschlag) infolge mächtiger Hypertonie (Blutdrucksteigerung) mit Herzerweiterung und Stauung in Leber, Milz und Nieren, und Lungenödem (Autopsie Prof. Löffler).» Eine Verschlechterung des Gesundheitszustandes des Propositus ist erst ungefähr 6 Monate vor seinem Tode – wohl an maligner Hypertonie – aufgetreten; er ließ sich jedoch nicht ärztlich behandeln.

Literaturangaben: HOESSLY-HAERLE, S. 307, 328, 366.

Aus der Korrespondenz von Dr. P. Emile WEIL mit der Familie des Propositus ist ersichtlich, daß der Arzt, ein damals bekannter Spezialist der Haemophilie, den Propositus in einer Veröffentlichung beschrieben hat. Es handelt sich möglicherweise um:

WEIL, Emile, 1910, La Cure de l'Hémophilie par le traitement sérique continu. Gazette médicale de Paris. Zit. nach HOESSLY-HAERLE (1930).

C XI. 643: Olga E., von Masein, geb. 1908; lebt in Davos (Z. Masein), kopuliert 1932 mit C XI. 642 Nikolaus C., von Davos, geb. 1899, lebt in Davos (Z. Davos).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 13. November 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C XI. 644: Franz E., von Masein, geb. 1909, † 1934 (Z. Masein).

Bluter: nach HOESSLY-HAERLE, S. 364, PIANTA, S. 172, und nach der von uns aufgenommenen Katamnese.

Katamnese (nach unserem Fragebogen S. 32–33 zusammengestellt):

Erste Manifestation der Blutungsbereitschaft bei dem Propositus im Alter von 4 Jahren anlässlich einer Tonsillektomie, vgl. HOESSLY-HAERLE, S. 364: «Franz (C XI. 644, Verf.) hatte laut ärztlichem Bericht nach einer Tonsillektomie und nach einer Zahnextraktion fast unstillbare Blutungen und auch öfters schon große Haematome».

Nach kleinen Verletzungen traten tagelange Blutungen und Nachblutungen auf.

Suffusionen kamen oft und nach geringen Ursachen vor.

Muskelblutungen sind mehrmals aufgetreten.

Nach Zahnextraktionen traten tagelang andauernde Blutungen auf. Der Propositus hatte auch oft tagelang anhaltende Zahnfleischblutungen.

Anhaltende Nasenblutungen sind mehrmals aufgetreten.

Gelenkblutungen sind in den Knie-, Ellenbogen- und Fußgelenken aufgetreten.

Der Propositus ist an einer Blutung des Darmtrakts verstorben. Teerstühle sind auch 3mal in früheren Jahren beobachtet worden (vgl. PIANTA, S. 172). Der Propositus litt zeitweise unter Schmerzen in den Nierenlogen, es wurde jedoch kein Blut im Harn beobachtet.

Blutungen im Zentralnervensystem sind nicht vorgekommen.

Literaturangaben: HOESSLY-HAERLE, S. 364; PIANTA, S. 172; FONIO, S. 82, Zeilen 1–4.

C XI. 648: Luzius E., von Masein, geb. 1917, lebt in Bretzwil, BL (Z. Masein),

kopuliert 1951 mit C XI. 649 Frieda Lisa B., geb. 1928, lebt in Bretzwil, BL (Z. Masein).

Bluter: nach HOESSLY-HAERLE, S. 364; PIANTA, S. 172–173; nach Angaben des behandelnden Arztes Dr. E. BONIFAZI. Thusis, nach gerinnungsphysiologischer Untersuchung von Dr. M. GEIGER (Gerinnungsphysiologisches Labor, Kantonsspital Zürich) und nach der von uns aufgenommenen Anamnese (nach unserem Fragebogen S. 32–33 zusammengestellt):

Erste Manifestation der Blutungsbereitschaft im Alter von 7 Jahren, als bei dem Probanden nach einem Sturz eine sehr starke und anhaltende Nasenblutung und ein großes Stirnhaematom aufgetreten sind.

In der Jugend des Probanden traten bei ihm anhaltende Blutungen

nach kleinen Verletzungen auf, heute ist die Blutungszeit nach Verletzungen annähernd normal.

Suffusionen traten besonders stark in der Jugend auf.

Muskelblutungen sind an den Beinen und an den Armen vorgekommen. letzte Blutung 1941 am Handrücken (Dr. BONIFAZI).

Beim Zahnwechsel traten starke Blutungen auf. Nach einer Zahnextraktion blutete der Proband einmal 14 Tage (vgl. PIANTA, S. 173). Auch Zahnfleischblutungen kamen in der Jugend vor.

Starke Nasenblutungen traten in der Jugend auf, im Frühling und im Herbst oft sogar täglich.

Gelenkblutungen sind mehrmals im re. Knie nach relativ leichten Traumata vorgekommen. Die letzte solche Blutung trat 1940 auf und wurde im Spital Thusis behandelt. Das re. Kniegelenk zeigt eine leichte morphologische Deformation auf, ohne Störung der Funktion.

1940 Nephritis mit Nierenblutung (Dr. BONIFAZI), der Proband berichtet über weinroten Harn während mehreren Tagen. Andere viscerale Blutungen sind nicht beobachtet worden.

Blutungen im Zentralnervensystem sind nicht aufgetreten.

1945 Blutung aus dem Gehörgang bei Trommelfellperforation (Dr. BONIFAZI). *Nach Aussage des behandelnden Arztes Dr. BONIFAZI sind seit dieser letzten Blutung bis zu unserer Bestandesaufnahme im Jahre 1956 keine Blutungserscheinungen mehr aufgetreten.*

Es sei hier zu bemerken, daß der Proband mit 28 Jahren seinen Coiffeurberuf infolge der damit verbundenen Verletzungsgefahr aufgegeben hat und Lehrer wurde. Der Proband bringt die Besserung seiner Blutungstendenz zum Teil mit dem Berufswechsel zusammen, da er sich als Lehrer besser schonen kann.

Gerinnungsphysiologische Untersuchung (siehe Seite 45–48) am 2. November 1956: Haemophilie B.

NB. Das Geburtsdatum des Probanden ist bei PIANTA irrtümlicherweise als 1919 und bei FONIO als 1910 angegeben.

PIANTA verwechselt Menga G. C X. 601, Mutter des Probanden, mit seiner Großmutter Barbara FELTSCHER, C IX. 378.

Literaturangaben: HOESSLY-HAERLE, S. 364; PIANTA, S. 172–173; FONIO, S. 82, Zeilen 5–9.

C XI. 654: (auch B XI. 511) Erika G., von Masein, geb. 1924, lebt in Masein (Z. Masein), kopuliert 1946 mit C XI. 653 (auch B XI. 510) Martin G., von Safien, geb. 1920, lebt in Masein (P. Z. Safien).

Die Probandin ist eine sichere Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 1. Oktober 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C XI. 657: Johannes B., von Zollikon/ZH. geb. 1920, lebt in Thusis (Z. Zollikon).

Bluter: nach HOESSLY-HAERLE, S. 364. Zeilen 34–40. Pianta, S. 173–175, nach der persönlichen Mitteilung der behandelnden Ärzte Dr. E. BONIFAZI, Thusis, und Dr. P. STEINER, Spital Thusis, nach gerinnungsphysiologischer Untersuchung von Dr. M. GEIGER (Gerinnungsphysiologisches Labor. Kantonsspital Zürich) und nach der von uns aufgenommenen Anamnese. Anamnese (nach unserem Fragebogen S. 32–33 zusammengestellt):

Erste Manifestation der Blutungsbereitschaft bei dem Probanden vor 1930, vgl. HOESSLY-HAERLE, S. 364: «Ein mächtiges Stirnhaematom, nach geringem Stoß, und öfteres Nasenbluten, sind bis jetzt (d. h. bis 1930, Verf.) die einzigen Anzeichen.» Genauere Angaben über diese frühesten Manifestationen sind nicht eruierbar.

Nach Verletzungen sind die Blutungserscheinungen relativ gering: 1945, Schnittverletzung am re. Zeigefinger, ohne jegliche Blutung (Dr. BONIFAZI). 1946, Panaritium ossale am li. Kleinfinger nach einer Quetschung, die zur Amputation im Fingermittelgelenk führte. Es kam dabei zu keiner besonderen Blutung. Eine solche trat aber auf, als nach 14 Tagen die Fäden entfernt wurden. Sie stand auf Kompression und eine kleine Transfusion (Dr. BONIFAZI). 1951, Verletzung am Handrücken ohne wesentliche Blutung (Dr. BONIFAZI).

Suffusionen sind nicht beobachtet worden.

Blutungen in die Muskulatur: 1939, anlässlich einer Lastwagenfahrt Blutung in die re. Oberschenkelmuskulatur und in das re. Knie- und Hüftgelenk, welche im Spital Thusis behandelt wurden; bei Spitalaufnahme war der Umfang des re. Oberschenkels 15 cm oberhalb des oberen Patellarandes um 13 cm größer als der des li. Oberschenkels; es wurde ebenfalls ein Muskelhaematom in der Adduktorenloge auf der Höhe des Os pubis festgestellt. 1942, erneutes Muskelhaematom im re. Oberschenkel. 1944, Muskelhaematom im li. Oberschenkel. 1945, Haematom im Handrücken. 1947, Muskelhaematom im re. Oberschenkel. 1948, Muskelhaematom im li. Oberschenkel (PIANTA, S. 175). 1951, Muskelhaematom im re. Oberschenkel. 1954, Spritzenhaematom nach Arovitinjektion. 1956, Muskelhaematom im re. Oberschenkel. Nach Angaben von Dr. BONIFAZI sind alle aufgeführten Muskelblutungen nach geringen Traumata entstanden.

Bei Zahnextraktionen kommt es nur manchmal zu Blutungen, die dann lediglich einige Stunden andauern, sonst sind aber keine anderen Blutungen aus dem Mund vorgekommen.

Nasenblutungen, die einige Stunden andauern, kommen von Zeit zu Zeit vor, vgl. auch die eingangs erwähnten Nasenblutungen in der Jugend des Probanden.

Gelenkblutungen: 1939, obenerwähnte Blutung in das re. Hüft- und Kniegelenk. Im gleichen Jahr ist noch eine Kniegelenkblutung aufgetreten, welche unter einer Gipshülse zum Stehen gebracht wurde (Dr. BONIFAZI). 1942, Kniegelenkblutung (Dr. BONIFAZI). 1948, Kniegelenkblutung li. nach geringem Trauma (PIANTA, S. 175).

1944, Nierenblutung. Haemoglobin bis 45° gesunken (Dr. BONIFAZI). 1953 Nierenblutung 14 Tage nach einer Tonsillitis (Dr. BONIFAZI). Sonst keine anderen visceralen Blutungen vorgekommen.

Blutungen im Zentralnervensystem sind nicht aufgetreten.

Zur Zeit der Bestandesaufnahme litt der Proband unter keinen Folgen der erfolgten Blutungen, doch wies das li. Bein am Ober- und Unterschenkel einen um 1 cm kleineren Umfang als das re. Bein auf, was als Folge der starken Blutung im Jahre 1939 (vgl. oben) aufgefaßt werden kann.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 13. August 1956: Haemophilie B.

Literaturangaben: HOESSLY-HAERLE, S. 364; PIANTA, S. 173–175; FONIO, S. 82, Zeilen 10–14.

C XI. 659: Erna B., von Zollikon, geb. 1922, lebt in Thusis (E. Thusis), kopuliert 1943 mit C XI. 658 Johann S., von Appenzell, geb. 1918, lebt in Thusis (E. Thusis).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 21. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C XI. 660: Silvia B., von Zollikon, geb. 1932, lebt in Masein (Z. Zollikon). Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 1. Oktober 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C XI. 663: Christina F., von St. Antönien, geb. 1923, lebt in Chur (E. Chur).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.
Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 2. Oktober 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C XI. 664: Katharina F., von St. Antönien, geb. 1928, lebt in Chur (E. Chur).
gleich wie bei C XI. 663.

C XI. 666: Nina B., von Versam, geb. 1919, lebt in Versam (P. Z. Ve.),
kopuliert 1942 mit C XI. 665 Hans B., von Versam, geb. 1910,
lebt in Versam (P. Z. Ve.).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.
Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 17. Juli 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C XI. 669: Hans C., von Valendas, geb. 1923, lebt in Tamins (P. Z. Val.),
kopuliert 1952 mit C XI. 670 Nina A., von Valendas, geb. 1926, lebt in Tamins (P. Z. Val.).

Der Proband wurde als Sohn einer sicheren Konduktorin (vgl. Tafel 5) untersucht.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 23. Oktober 1957: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C XI. 671: Christina C., von Valendas, geb. 1925, lebt in Valendas (P. Z. Val.).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 5 und 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 13. November 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C XI. 672: Balthasar C., von Valendas, geb. 1929, † 1935 (P. Z. Val.).
Bluter: nach HOESSLY-HAERLE, S. 365, Nachtrag, PIANTA, S. 171, und nach den 1934 von uns (G. TRUOG) gemachten Beobachtungen.

Katamnese (nach unserem Fragebogen, S. 32–33 zusammengestellt):

Erste Manifestation der Blutungserscheinungen bei dem Propositus im Alter von 1 Jahr, als er infolge einer unstillbaren Blutung aus dem Frenulum

der Oberlippe ins Kreuzspital Chur eingeliefert wurde. Die Blutung entstand durch Anstoßen an einem harten Gegenstand und dauerte 8 Tage bis sie im Spital durch eine Transfusion gestillt wurde. Man stellte zu gleicher Zeit eine starke Suffusion an der Stirne fest. Die Eltern berichteten, daß bei dem Propositus schon während des 1. Lebensjahres des öfteren Suffusionen nach geringen Ursachen aufgetreten seien.

Verletzungen wurden außer der oben beschriebenen Mundverletzung nicht beobachtet.

Suffusionen traten sehr oft und nach geringen Ursachen, wie z. B. etwas brüskes Anfassen am Arm auf.

Haematome in der Muskulatur sind einige Male aufgetreten.

Blutungen aus der Gingiva traten oft auf und dauerten tagelang, mehrmals bis eine Woche.

Nasenblutungen sind mehrmals aufgetreten, sie hielten jeweils mehrere Tage an.

1934, Haemarthros im re. Sprunggelenk (siehe weiter unten).

Viscerale Blutungen konnten nicht beobachtet werden, jedoch hatte der Propositus öfters einen pechschwarzen Stuhl, welcher aber auch durch das bei Zahnblutung verschluckte Blut verursacht werden konnte.

Blutungen im Zentralnervensystem sind nicht aufgetreten.

1934 ist der Propositus zu uns in Behandlung gekommen:

17. April 1934, Haemarthros im re. Sprunggelenk (vgl. oben) und multiple Hautsuffusionen.

7. August 1934, großes Haematom mit oberflächlicher Hautschürfung am re. Jochbogen.

4. Dezember 1934, Haemoglobin 18%, Patient litt nach Aussagen der Eltern vor einiger Zeit an leichtem Nasenbluten.

24. Dezember 1934, Zahnfleischblutung, die bis zum 27. Dezember anhielt und am 29. wieder einsetzte, worauf am 31. Einweisung ins Kreuzspital Chur. Exitus am 1. Januar 1935 an Verblutung.

NB.: Das Geburtsdatum des Propositus ist bei PIANA irrtümlicherweise als 1935 und das Todesdatum als 31.12.1943 angegeben.

Literaturangaben: HOESSLY-HAERLE, S. 365, als Nachtrag; PIANA, S. 171–172; FONIO, S. 81, Zeilen 44–46.

C XI. 673: Katharina C., von Valendas, geb. 1935, lebt in Valendas (P. Z. Val.).

gleich wie bei C XI. 671, jedoch gerinnungsphysiologische Untersuchung am 2. September 1956.

C XII. 177: Olga C., von Davos, geb. 1933, lebt in Davos (Z. Davos).
kopuliert 1954 mit C XII. 176 Andreas F., von Wartau, SG,
geb. 1925, lebt in Davos (Z. Wartau).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 13. November 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C XII. 178: Hulda C., von Davos, geb. 1939, lebt in Davos (Z. Davos).
gleich wie bei C XII. 177.

C XII. 183: Erich E., von Masein, geb. 1941, lebt in Zürich (Z. Masein).
Der Proband wurde als Sohn einer möglichen Konduktorin (vgl. Tafel 6)
untersucht. Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am
8. August 1957: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C XII. 185: Arnold Leonhard G., von Safien, geb. 1948, lebt in Masein
(Z. Masein und Z. Safien).

Bluter: nach Diagnose der behandelnden Ärzte Dr. P. STEINER und Dr.
J. VERAGUT, Thuisis, und nach der von uns aufgenommenen Anamnese.
Anamnese (nach unserem Fragebogen, S. 32–33, zusammengestellt):

Erste Manifestationen der Blutungsbereitschaft im 2. Lebensjahr, als
bei dem Probanden große Suffusionen nach Umfällen auftraten.

Suffusionen treten oft auf, auch nach geringen Traumata.

Weichteilblutungen sind nicht beobachtet worden.

Der Zahnwechsel ist ohne abnorme Blutungen verlaufen. Einmal trat
eine 5 Tage dauernde Sickerblutung aus einer Zahntasche (Paradentitis) auf.

Nasenblutungen sind nicht vorgekommen.

Eine Kniegelenkblutung ist 1955 nach einem Sturz beim Skifahren auf-
getreten. Es kam zu einer starken Schwellung und Schmerzen, die 6
Wochen andauerten, erst nach 1 Jahr sind die Beschwerden völlig abge-
klungen. Ende 1956 Haemarthros im Ellbogen re. (Dr. VERAGUT). Beide
Gelenkblutungen haben keine bleibenden Folgen hinterlassen.

Viscerale Blutungen und Blutungen im Zentralnervensystem sind nicht
aufgetreten.

Gerinnungsphysiologische Untersuchung wurde nicht durchgeführt, da
die Familie des Probanden mit der Blutentnahme nicht einverstanden war.

Literaturangaben: nicht beschrieben.

C XII. 187: Johann S., von Appenzell, geb. 1943, lebt in Thusis
(E. Thusis).

Der Proband wurde als Sohn einer möglichen Konduktorin (vgl. Tafel 6) untersucht. Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 21. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C XII. 188: Marianne S., von Appenzell, geb. 1944, lebt in Thusis
(E. Thusis).

Die Probandin ist eine mögliche Konduktorin, wie aus Tafel 6 ersichtlich. Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 21. September 1956: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

C XII. 189: Markus S., von Appenzell, geb. 1946, lebt in Thusis
(E. Thusis)

gleich wie bei C XII. 187.

C XII. 190: Ernesto S., von Appenzell, geb. 1949, lebt in Thusis
(E. Thusis).

gleich wie bei C XII. 187.

C XII. 191: Hans B., von Versam, geb. 1943, lebt in Versam (P.Z. Ve.). Der Proband wurde als Sohn einer möglichen Konduktorin (vgl. Tafel 6) untersucht.

Gerinnungsphysiologische Untersuchung (siehe S. 45–48) am 23. Oktober 1957: normale Gerinnungswerte.

Literaturangaben: nicht beschrieben.

5. Nachforschungen über die Abstammung der 3 haemophilen Brüder J.

In seinen Mitteilungen an GRANDIDIER (1877), S. 65, bringt VIELI 3 haemophile Brüder J. aus Chur in Zusammenhang mit dem Tenner Bluterstamm, ohne jedoch die gemeinsame Abstammung beweisen zu können. HOESSLI (1885), S. 26–27, berichtet über seine ergebnislosen Nachforschungen, um diese 3 Bluter mit Tenna in Verbindung zu bringen. BULLOCH und FILDES (1912) übernehmen sie ebenfalls in ihre Beschreibung der Bluter

von Tenna und werden darin auch von HOESSLY-HAERLE (1930), S. 325, befolgt.

Wir haben uns bemüht, die Frage der Abstammung dieser 3 haemophilen Brüder abzuklären, und zwar soweit wie dies nur irgendwie anhand der vorhandenen Quellen möglich ist. Zu diesem Zwecke benützten wir alle in Frage kommenden Zivilstandsregister- und Kirchenbücherangaben sowie auch sämtliche vorliegenden Archivquellen.

Die Vorfahren der Propositi wurden nicht nur mütterlicherseits in der Frauenlinie, sondern auch väterlicherseits zurückverfolgt und in einer Ahnentafel zusammengestellt. Wir bezweckten damit das Erfassen auch der eventuellen männlichen haemophilen Vorfahren, aus der Überlegung heraus, daß wenn z. B. der Großvater mütterlicherseits ein bis jetzt nicht erfaßter Bluter gewesen sein sollte, die Haemophilie, wenn nicht bei ihm, so vielleicht bei seinen Brüdern oder in der Generation seines Großvaters, aus den zeitgenössischen Archivquellen erfaßbar sein könnte.

Unsere Nachforschungen konnten besonders vollständig gestaltet werden dank der ausgeprägten Familientradition bei den heute lebenden Nachkommen der Familie J. Frl. Margarete J., geb. 1890 (vgl. Tafel 4) besitzt in ihrer bedeutenden Privatsammlung ein reiches Familienarchiv und ist uns mit zahlreichen Angaben behilflich gewesen. Da die Familie J. mit Patriziergeschlechtern Graubündens verwandt ist, war ein genaueres Zurückverfolgen ihrer Vorfahren anhand der lokalgeschichtlichen Angaben möglich.

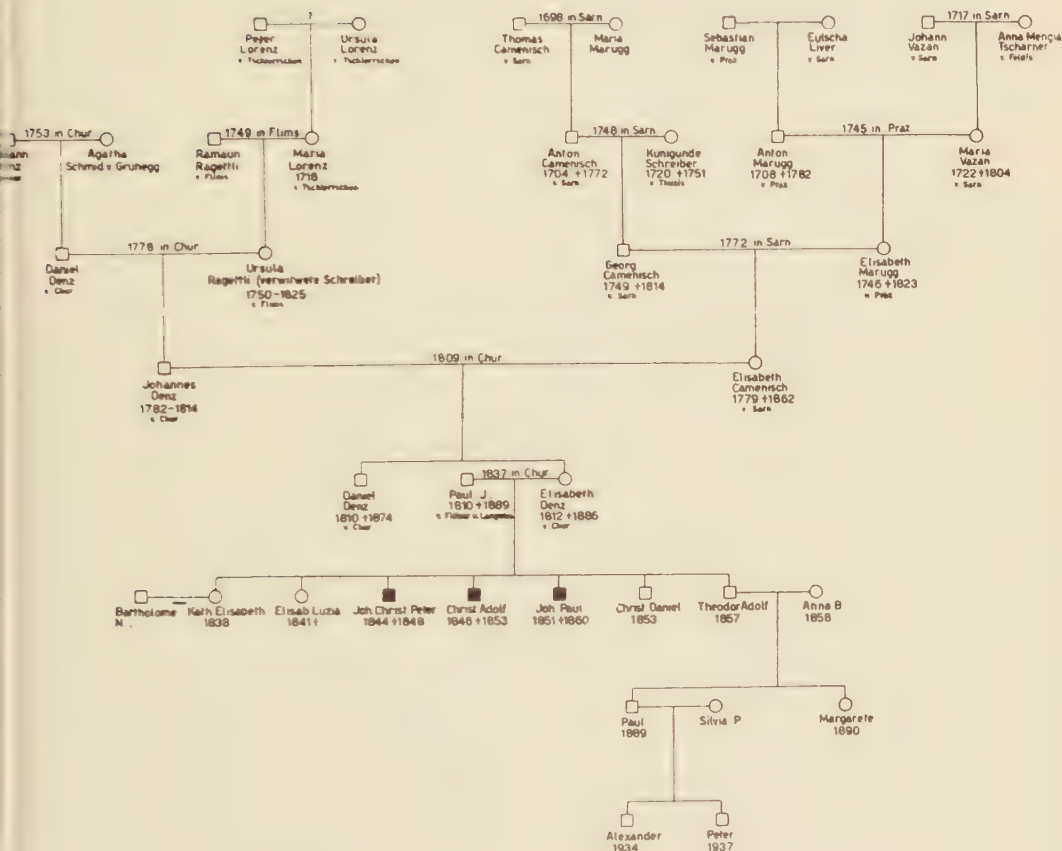
Vorerst konnte festgestellt werden, daß der Onkel mütterlicherseits der 3 Bluterbrüder, Daniel DENZ, von Chur, geb. 1810, † 1874 (K. Chur), kein Haemophiler gewesen ist. Als solcher wäre er sonst auch von seinem Zeitgenossen HOESSLI (1885, vgl. S. 27) erwähnt, der die verwandtschaftlichen Zusammenhänge in der Familie J. in bezug auf Haemophilie eingehend untersucht hatte. Es liegen keine Indizien vor, daß der Großvater der Propositi, Johannes DENZ, von Chur, geb. 1772, † 1814 (K. Chur) an Haemophilie gelitten hat. Er ist Schmied gewesen, ein Beruf mit hoher Verletzungsgefahr, der von einem Bluter wohl nicht ergriffen worden wäre. Nach einer ausführlichen Zeitungsnotiz im «Der Telegraph für Graubünden», Nr. 39 vom 17. Mai 1814, welche am 7. Mai 1814 von seinem Vater Daniel an die Zeitung übergeben wurde, ist Johannes DENZ an einer Infektionskrankheit gestorben, die damals in Chur herrschte. In den noch früheren Generationen kommen wir mit den SCHMID von GRÜNEGG in ein bekanntes Bündner Patriziergeschlecht. Desgleichen bei den Vorfahren der Elisabeth CAMENISCH, von Sarn, geb. 1779, † 1862 (K. Sarn), da die CAMENISCH und MARUGG (vgl. Tafel 4) zu den Patriziergeschlechtern am Heinzenberg in

Tafel 4 AHNENTAFEL DER MUTTER DER DREI BLUTER J. IN CHUR

Nach Familientradition in Zusammenhang mit den Blutern von Tenna. Genealogische Verbindung nicht auffindbar

ANCESTORS TABLE OF THE MOTHER OF 3 HEMOPHILIACS J IN CORE

According to family tradition descendants of Tenna Hemophilic. Genealogical connection not findable



Anmerkung: lies *Vazau* statt *Vazan*.

Graubünden zählten. Bei dem bedeutenden Umfang der über diese Geschlechter vorliegenden Archivquellen kann mit großer Wahrscheinlichkeit angenommen werden, daß eventuelle Haemophiliefälle nicht unerwähnt geblieben wären. Solche sind aber weder in den damaligen Beschreibungen zu finden, noch sind sie bei den weiteren uns bekannten Nachkommen aufgetreten.

Es scheint also, daß im Falle der 3 haemophilen Brüder J. eine *Mutation* zur *Haemophilie* ohne einen nachweisbaren Erbgang aufgetreten ist. Eine genealogische Verbindung zu Tenna läßt sich anhand der vorliegenden Quellen nicht feststellen, die *Vererbung der Haemophilie aus dem Tenner Bluterstamm kann jedenfalls mit großer Wahrscheinlichkeit verneint werden*. Es liegen auch keine Anhaltspunkte für die Möglichkeit einer solchen Vererbung auf illegitimem Wege vor.

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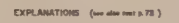
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LEGENDE (siehe auch Text S. 78)



EXPLANATIONS (see also cont p. 72)



BLUTERSTAMM VON TENNA um 1650-1955

NACHFAHRENTAFEL. Teil A

HEMOPHILIACS OF TENNA about 1850-1955
DESCENDANTS' TABLE. Part A

Angenommener Vererbungsweg
wahrscheinlicher Vererbungsweg

■ mutmasslicher Bluter C V. 74 siehe speziellen Teil der Arbeit

... illegitimes Kind

☐ ☐ Ehepaar ohne Nachkommen


☐ ☐ ☒ nicht weiterverfolgbares Ehepaar bzw. Einzelperson
☐ ☐ ☒ nicht weiterverfolgtes Ehepaar bzw. Einzelperson

☒ ☒ ☐ weiterverfolgte Auswanderer (Emigranten) mit Nachkommen und Angehörigen.

☐ ☐ ☐ nicht weiterverfolgbare Auswanderer (Emigranten)

Die als Nachtrag mit kleinen Buchstaben oder mit * versehene Standortnummern unterscheiden sich in nichts von den übrigen Posten der Nachfahrntafel

 Presumptive way of translation
 Probable way of translation


 Presumptive homologies: C 12.34 see descriptive part of study

△	Still-born or premature birth, sex unknown			
♂	0	1	1	0
♀	1	0	0	1

Diagrama 1

 Children's code

Married couple recorded at time of their marriage and unchangeable thereafter

 Married couple related to him or their marriage will follow up discontinued through lines of investigation

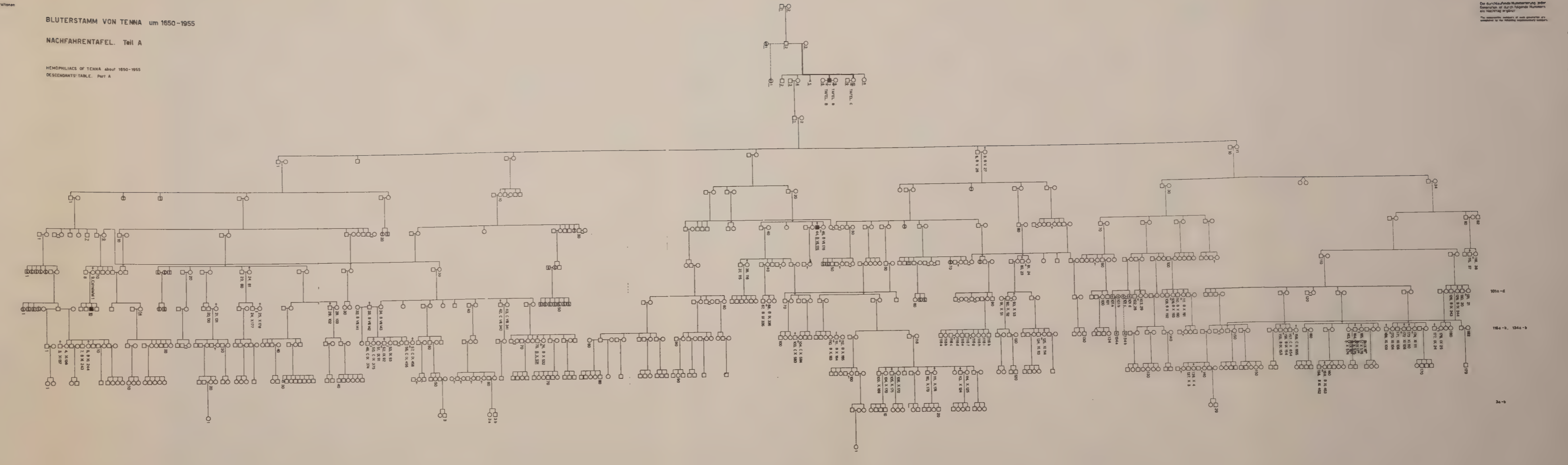
Y Single persons recorded at birth but follow up discontinued through City of Investigation

E-C E Estimated an unknown number of members with their parents

Emigrants irretrievable after Nazi expropriation

The names marked by leading authors having small letters or ® signs

included after the essential part of descendants' table was designed. They differ in no way from the other items of the table.



101a-d

118a -k, 1134a -b

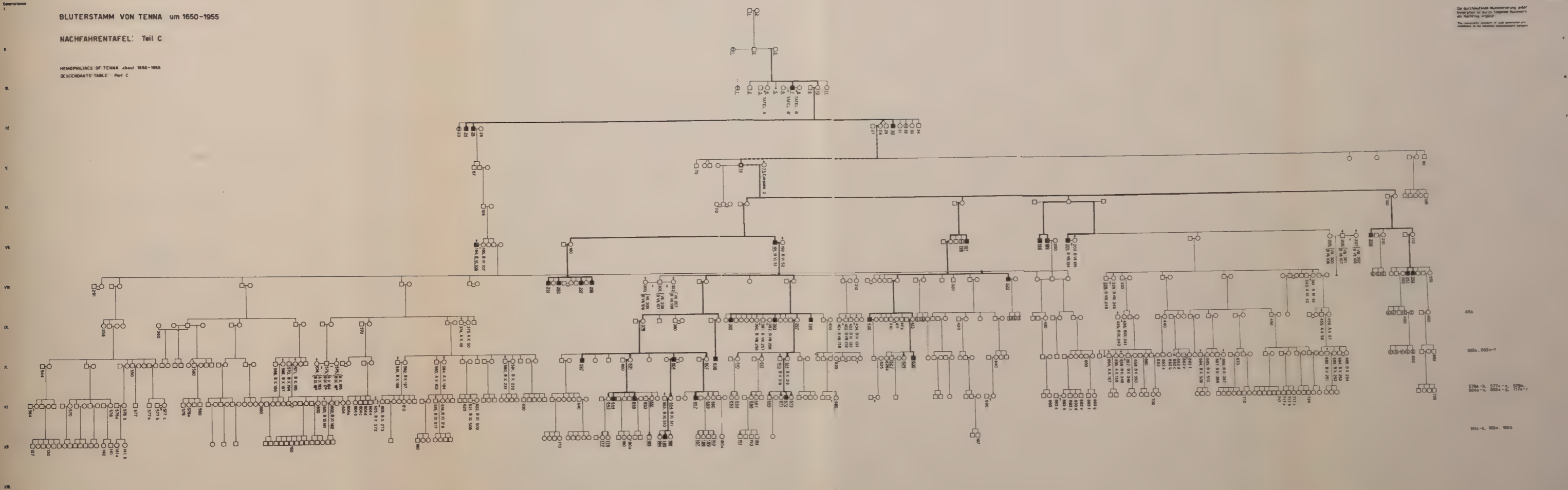
34-b

Generations

BLUTERSTAMM VON TENNA um 1650-1955

NACHFAHRENTAFEL: Teil C

HEMOPHILIACS OF TENNA about 1650-1955
DESCENDANTS' TABLE: Part C



Die durchlaufende Nummerierung jeder
Einzelperson ist durch die folgende Nummer
als "NACHFAHRENTAFEL" gegeben.
The continuous numbering of each generation is
indicated by the following "NACHFAHRENTAFEL" number.

Generations

I

II

III

IV

V

VI

VII

VIII

IX

X

XI

XII

XIII



Tafel 5 UEBERSICHT UEBER DIE NACHFAHRENTAFEL DES BLUTERSTAMMES VON TENNA

Sämtliche Bluter, sichere Konkudrinnen und ihre Geschwisterschaften, nach Geburtsjahren geordnet

○ sichere Konkudrinnen

97 Standortnummer in der Nachfahrenafel

1791 Geburtsjahr
1836 Todesjahr, wenn nicht angegeben, 1956 am Leben,
† als Neugeborenes gestorben

■ Bluter
Nachkommen in der Nachfahrenafel verfolgbar,
darunter keine Bluterfälle bekannt

458 → Geburt weiterer Geschwister möglich, Mutter im Fort-
pflanzungsalter (geboren nach 1906)

□ mutmasslicher Bluter C.V.74, siehe speziellen Teil der Arbeit

△ Totgeburt

SYNOPSIS OF DESCENDANTS' TABLE OF HEMOPHILIACS OF TENNA

all Hemophiliacs, Known Carriers and their Sibships recorded in Rank of Birth

○ Known carrier

97 Location number in descendants' table

1791 Year of birth
1836 Year of death; if not stated, person alive in 1956,
† = deceased before completion of 1st year of life

■ Hemophilic
Progeny traceable in descendants' table, no hemophiliacs
known among these

458 → Birth of further brothers and sisters possible, mother in
procreative age (born after 1906)

□ Presumptive hemophilic C.V.74, see descriptive part of study

△ Still-birth

Generationen

I

II

IV

V

VI

VII

VIII

IX

X

XI

XII

Generationen

II

III

IV

V

VI

VII

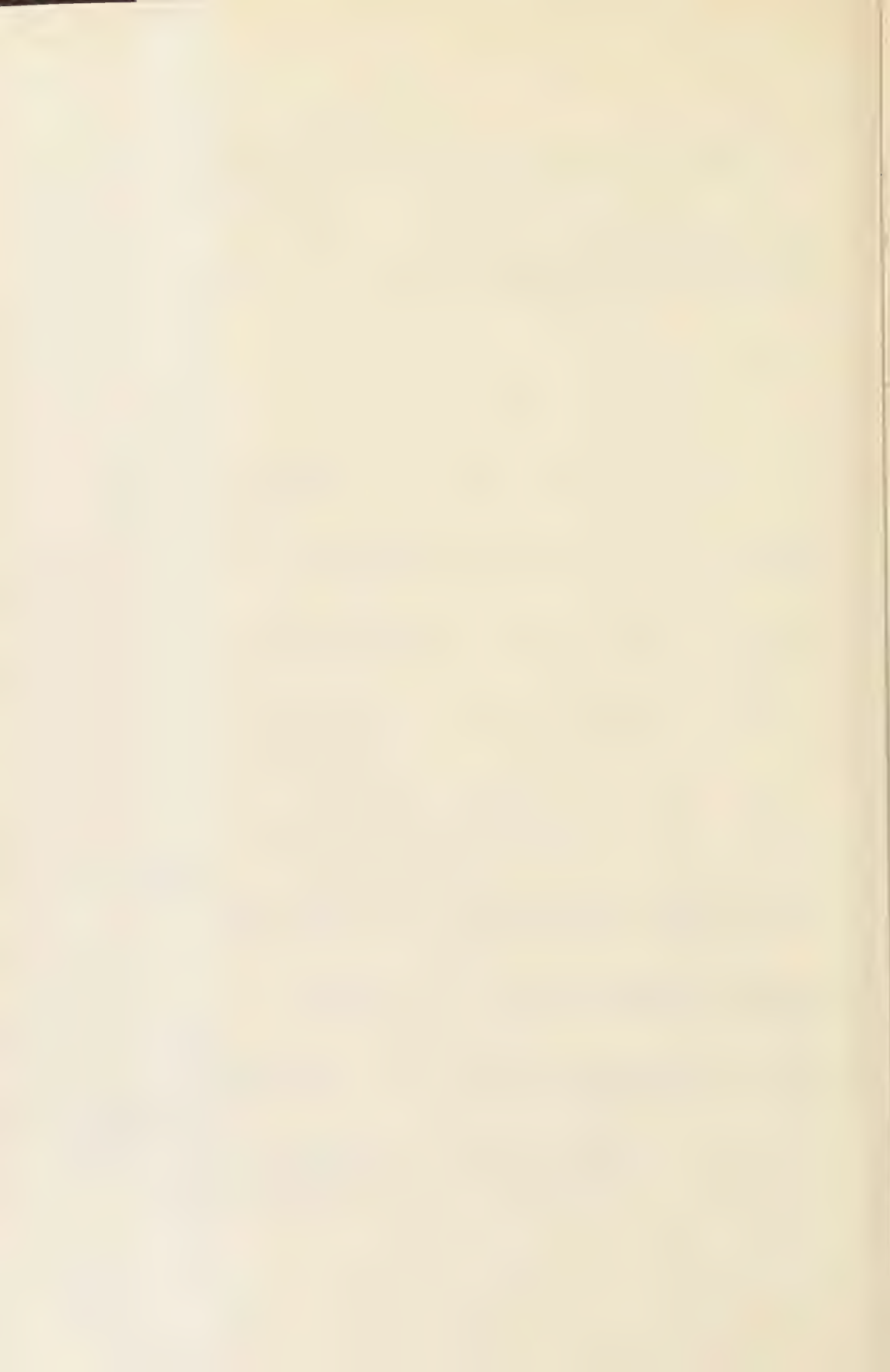
VIII

IX

X

XI

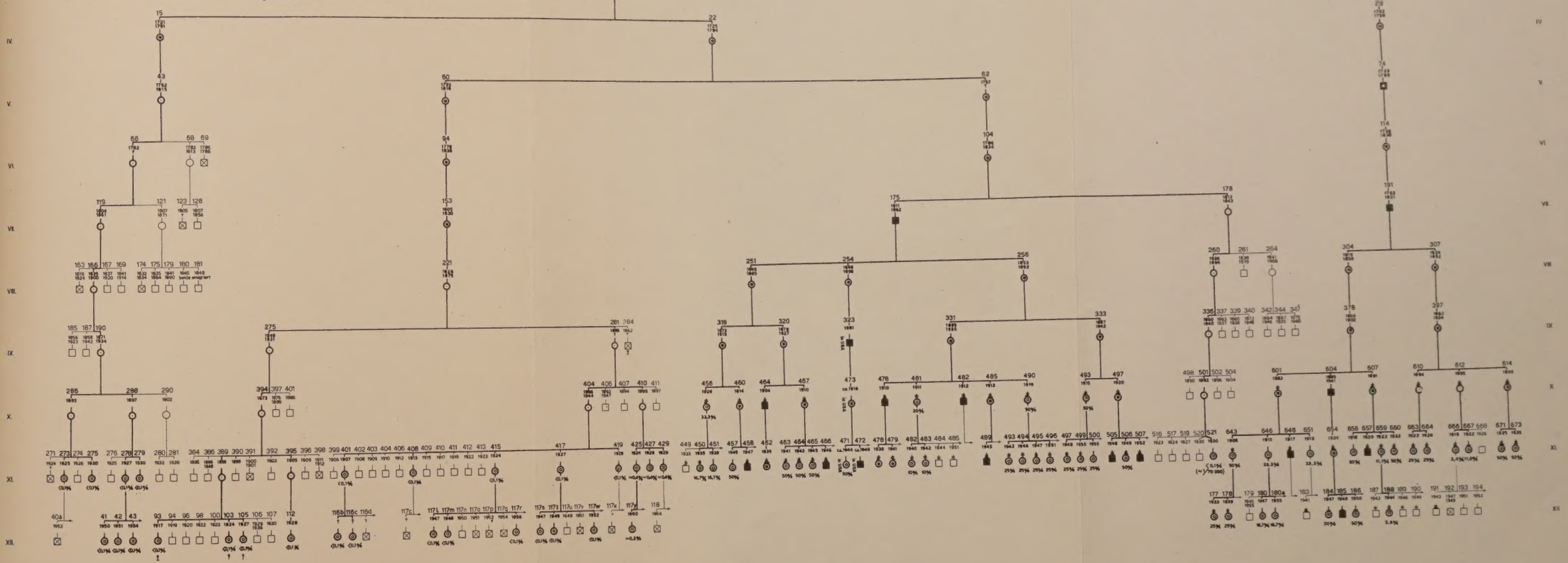
XII



Tafel 6
MÖGLICHKEITEN VON WEITERVERERBUNG DER HAEMOPHILIE BEI DEN IM JAHRE 1956 LEBENDEN
NACHKOMMEN DES BLUTERSTAMMES VON TENNA

Unter den Geschwistern sind nur die für die Weitervererbung bzw. für die Wahrscheinlichkeitsberechnung (siehe S. 53) in Frage kommenden Personen nach Geburtsjahre geordnet angegeben.
Dick gezeichnet: möglicher Weitervererbungsweg bis 1956 und alle Fälle mit Möglichkeit von Weitervererbung der Haemophilie
Dünne gezeichnet: lediglich zur Schilderung der Wahrscheinlichkeitsberechnung angegebene Fälle

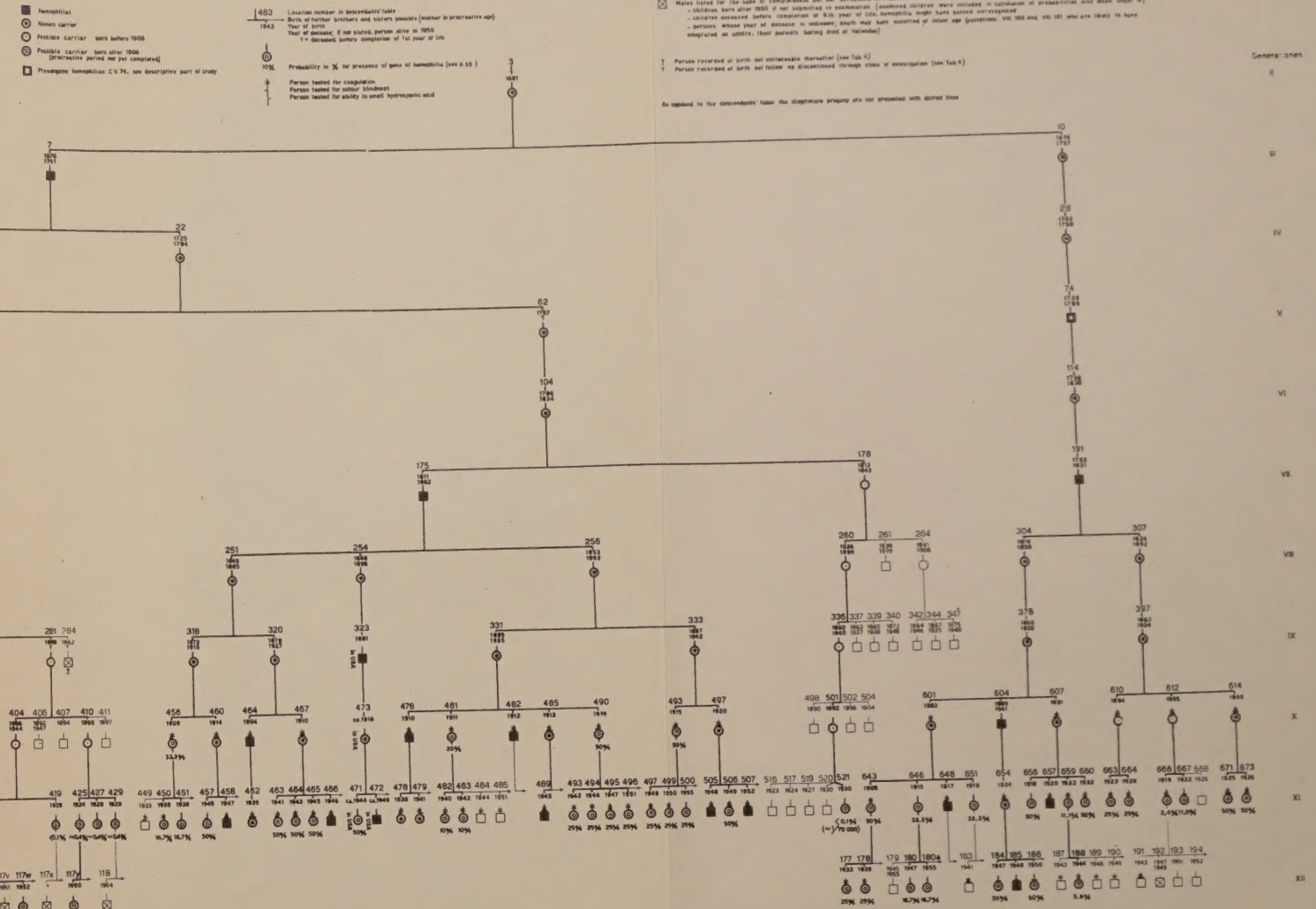
- Bluter
○ sichere Konkubitorin
○ mögliche Konkubitorin geboren vor 1906
○ mögliche Konkubitorin geboren nach 1906 (Fortpflanzungsperiode nach nicht abgeschlossener)
■ mütterlicher Bluter C.V. 74, spez. Teil der Arbeit
- 483 Standortnummer in der Nachfahrenstafel
Geburtsjahr
Todesjahr, wenn nicht angegeben, 1956 am Leben,
† = als Neugeborenes gestorben
- 154 Wahrscheinlichkeit in % für das Vorhandensein des Haemophiliegens (siehe S. 53)
- 1 nicht weiterverfolgbare Person (siehe Tab. 4)
† nicht weiterverfolgte Person (siehe Tab. 4)
† gerichtsphysiologisch untersuchte Person
† auf fürbündelndem untersuchte Person
† auf CH-Geruchstest untersuchte Person
- im Gegensatz zur Nachfahrenstafel sind die illegitimen Nachkommen nicht gestrichelt gezeichnet



POSSIBILITIES OF FURTHER TRANSMISSION OF HEMOPHILIA IN DESCENDANTS OF HEMOPHILIACS ALIVE IN 1956. EXTRACT FROM DESCENDANTS' TABLE OF HEMOPHILIACS OF TENNA

Among the 530s are listed in rank of birth only the persons relevant for transmission and for calculation of probabilities (see S. 53)

This printing: possible way of transmission of hemophilia up to 1956 and all contemporary status with possibility of transmission
Thin printing: cases used for calculation of probabilities only



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